UNIVERSITI PUTRA MALAYSIA

VITAMIN D RECEPTOR, INTERLEUKIN 12B AND INTERLEUKIN 23R GENE POLYMORPHISMS AND RISK OF CHRONIC PLAQUE PSORIASIS AMONG PATIENTS IN A MALAYSIAN HOSPITAL

NUR SYAZANA BINTI MATNOR

FPSK(M) 2017 54

VITAMIN D RECEPTOR, INTERLEUKIN 12B AND INTERLEUKIN 23R GENE POLYMORPHISMS AND RISK OF CHRONIC PLAQUE PSORIASIS AMONG PATIENTS IN A MALAYSIAN HOSPITAL

By

NUR SYAZANA BINTI MATNOR

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the Degree of Master of Science

March 2017

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Master of Science

VITAMIN D RECEPTOR, INTERLEUKIN 12B AND INTERLEUKIN 23R GENE POLYMORPHISMS AND RISK OF CHRONIC PLAQUE PSORIASIS AMONG PATIENTS IN A MALAYSIAN HOSPITAL

By

NUR SYAZANA MATNOR

March 2017

Chair: Kartini Farah binti Abdul Rahim, PhD
Faculty: Medicine and Health Sciences

Background: Psoriasis is a non-contagious chronic inflammatory disease that primarily affecting the skin and can manifests to joints. The underlying etiology of the disease involves a complex interaction of environment, genetic and immunological factors. Previous studies have reported that inflammatory cytokines are found to be elevated in psoriasis patients. Meanwhile, vitamin D has shown to be an effective treatment for psoriasis but the effectiveness is different between patients. Genetic plays an important role in the pathogenesis of disease and a number of single nucleotide polymorphisms (SNPs) on interleukin 12B (*IL12B*), interleukin 23R (*IL23R*) and vitamin D receptor (*VDR*) genes have been identified. However, the role of these SNPs on the phenotypic expression of psoriasis is still under investigation and none has been done on Malaysian population.

Objectives: This study aimed to investigate the association of SNPs of *VDR*, *IL12B* and *IL23R* genes on risk of chronic plaque psoriasis with adjustment for potential confounders such as age, gender, body mass index (BMI), and severity of psoriasis. The interaction between the gene polymorphisms and age of disease onset as well as the severity of the disease on the patients were also assessed.

Methods: In this study, a hospital based case control study comprised of 101 chronic plaque psoriasis patients and 99 healthy normal individuals was conducted. Socio-demographic data was recorded for both groups with additional Psoriasis Area Severity Index (PASI) and Dermatology Life Quality Index (DLQI) from psoriasis patients. Extracted DNA was amplified by polymerase chain reaction (PCR) reaction and genotyped for SNP by restriction fragment length polymorphism (RFLP) analysis. Genotype distribution and allelic frequencies were compared between patients and controls. Mean values and odds ratios (ORs) with 95% confidence interval (CI) were calculated using SPSS software (version 19.0)

Results: A/C carriers of rs7975232 polymorphism of *VDR* gene significantly increase the risk of psoriasis (OR 2.049, 95% CI 1.006-4.172, p = 0.048). No significant association reported for polymorphisms of *IL12B* and *IL23R* genotypes with risk of psoriasis. C/T carriers of *IL23R* gene decrease the risk of psoriasis but the result is not significant. Also no significant association reported with gender, race and lifestyle habits including cigarette smoking, alcohol consumption and BMI with risk of psoriasis.

Conclusion: Association of rs7975232 polymorphism with chronic plaque psoriasis in Malaysian population shows similarity from previous similar study that had been done in Asian population. This is the first association of selected polymorphisms from various genes conducted in Malaysian population for chronic plaque psoriasis. Such finding might be able to contribute to understand the various responses and resistance to vitamin D therapy in psoriasis and might allow us a step closer in solving the complexity of chronic plaque psoriasis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

POLIMORPHISME GEN BAGI VITAMIN D RECEPTOR, INTERLEUKIN 12B DAN INTERLEUKIN 23R DENGAN FAKTOR RISIKO PSORIASIS VULGARIS DALAM KALANGAN PESAKIT-PESAKIT DI HOSPITAL DI MALAYSIA

Oleh

NUR SYAZANA MATNOR

Mac 2017

Pengerusi: Kartini Farah binti Abdul Rahim, PhD
Fakulti: Perubatan dan Sains Kesihatan

Latar belakang: Psoriasis adalah penyakit keradangan kronik yang tidak berjangkit dan selalunya terjadi ke atas kulit namun juga boleh merebak ke bahagian sendi, kuku dan kulit kepala. Proses penyakit ini melibatkan interaksi kompleks antara alam sekitar, genetik dan juga faktor imunologi. Kajian-kajian yang pernah dilakukan telah menunjukkan peningkatan jumlah sitokin inflamasi sebagai salah satu proses psoriasis. Manakala vitamin D pula telah dibuktikan sebagai salah satu rawatan untuk penyakit ini namun demikian kesan rawatan dilaporkan berbeza untuk setiap pesakit. Genetik memainkan peranan penting dalam patogenesis psoriasis dan sejumlah polimorfisme nukleotida tunggal telah dikenal pasti pada gen seperti interleukin 12B (*IL12B*), interleukin 23R (*IL23R*) dan vitamin D reseptor (*VDR*). Walaupun begitu, peranan yang dimainkan oleh setiap polimorfisme ini terhadap pemaparan fenotip untuk psoriasis adalah masih dalam kajian dan tidak ada hasil kajian dilaporkan untuk populasi Malaysia.

Matlamat: Kajian ini bertujuan untuk mengkaji hubungan antara polimorfisme nukleotida tunggal bagi gen *IL12B*, *IL23R* dan *VDR* dengan risiko penyakit psoriasis dan dalam masa yang sama faktor seperti umur, jantina, indeks jisim badan, dan tahap keterukan penyakit psoriasis juga akan diambil kira. Kajian ini juga akan menyelidik interaksi antara polimorfisme gen dengan umur pesakit ketika pertama kali psoriasis timbul dan juga tahap keterukan penyakit ini kepada pesakit.

Kaedah: Kajian ini adalah kajian kes kontrol bersandarkan hospital dan merangkumi 101 pesakit plak psoriasis dan 99 individual yang sihat. Data sosio-demografik direkodkan untuk kedua-dua kumpulan ditambah dengan keputusan PASI dan DLQI daripada kumpulan psoriasis. DNA yang diekstrak daripada sampel darah akan melalui proses PCR dan RFLP. Pengedaran genotip dan frekuensi alel akan dibandingkan

antara dua kumpulan tersebut. Nilai purata dan nisbah kemungkinan dengan 95% selang keyakinan akan dihitung menggunakan perisian SPSS.

Keputusan: Kajian ini melaporkan pembawa alel A/C untuk rs7975232 polimorfisme gen *VDR* mempunyai lebih risiko untuk mendapat penyakit psoriasis. Tiada hasil yang signifikan dilaporkan untuk polimorfisme gen *IL12B* dan *IL23R*. Pembawa alel C/T bagi gen *IL23R* dilaporkan kurang risiko untuk terkena psoriasis tapi keputusan ini adalah tidak signifikan. Tiada laporan signifikan daripada analisis data sosio-demografik dan hubungan dengan risiko psoriasis.

Kesimpulan: Hubungan antara polimorfisme rs7975232 dengan psoriasis dalam populasi Malaysia daripada kajian ini menunjukkan persamaan yang sama dengan kajian-kajian yang telah dilakukan dengan populasi Asia. Kajian ini merupakan kajian pertama yang dilakukan di Malaysia dalam mengenal pasti hubungan antara polimorfisme gen-gen terpilih dengan risiko untuk mendapat psoriasis. Hasil daripada kajian ini mungkin dapat membantu untuk lebih memahami tindak balas pelbagai dan rintangan terhadap terapi vitamin D yang ditunjukkan oleh pesakit psoriasis dan juga mungkin boleh membantu merungkai misteri penyakit psoriasis.

ACKNOWLEDGEMENTS

I would like to congratulate myself for finally finishing my dissertation, despite the many delays especially during sample collection, the worst ever. Heartfelt thanks to my main supervisor, Dr. Kartini Farah Rahim, for her generous heart and for being so understanding and patience. I know how very busy you are doctor, so thank you for still making time for me whenever I asked of you. Thank you for helping me especially during the hospital visit, if you weren't around the sample collection will not be as smooth as how it been.

Thank you to my co-supervisors, Prof. Lye Munn Sann for guiding my thesis writing so I won't stray too far off and to Prof. Rozita for helping us finding the right direction at the beginning of the study. Thank you to all the staffs from Dermatology Clinic Hospital Serdang especially Kak Azimah and Kak Halimatun for assisting me during the sample collection, for being so kind as to come whenever I need their help. To the staffs from general blood collection of Hospital Serdang, thank you for your help so I can collect all my samples in such a short (a week) time.

To my labmate and closest friend, Nurulassikin, such a massive help you are, we went through so many things together for the last years, I'm not really sure I can go through everything again alone. Ban and Allan, thank you for guiding me whenever I need help with all the lab works. And last, to my siblings and my parents, for never giving up on me, thank you all!

I certify that a Thesis Examination Committee has met on 15 March 2017 to conduct the final examination of Nur Syazana binti Matnor on her thesis entitled "Vitamin D Receptor, Interleukin 12B and Interleukin 23R Gene Polymorphisms and Risk of Chronic Plaque Psoriasis among Patients in a Malaysian Hospital" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Johnson Stanslas, PhD
Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Chairman)

Loh Su Peng, PhD
Associate Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Internal Examiner)

Azlina Ahmad Annuar, PhD
Senior Lecturer
Universiti Malaya
Malaysia
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 2 June 2017

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Kartini Farah binti Abdul Rahim
Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Lye Munn-Sann, PhD
Professor (Medical)
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Rozita binti Rosli, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

_____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No: Nur Syazana Binti Matnor (GS37625)

Declaration by Members of Supervisory Committee

This is to confirm that:

- The research conducted and the writing of this thesis was under our supervision;
- Supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of
Supervisory Committee: Dr. Kartini Farah binti Abdul Rahim

Signature: _____
Name of Member of
Supervisory Committee: Prof. Dato, Dr. Lye Munn-Sann

Signature: _____
Name of Member of
Supervisory Committee: Prof. Dr. Rozita binti Rosli

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BSA	Body Surface Area
DLQI	Dermatology Life Quality Index
GWAS	Genome Wide Association Studies
HLA	Human Leukocyte Antigen
HWE	Hardy-Weinberg Equilibrium
IL	Interleukin
MHC	Major Histocompatibility Complex
PASI	Psoriasis Area Severity Index
RFLP	Restriction Fragment Length Polymorphism
SNP	Single Nucleotide Polymorphism
VDR	Vitamin D Receptor

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Psoriasis is a common, non-contagious, chronic, inflammatory disease that primarily affecting the skin and can manifest itself in the joints, nails and scalp. It can be characterized by localized or widespread lesions known as plaques. These plaques are the results of abnormal proliferation and differentiation of the keratinocytes of the skin. The classical presentation of the plaques are thick, red and scaly rash which can be itchy and painful (Langley et al., 2005). Although non-fatal, this disease can cause distressing conditions that has negative impact on patient's health and quality of life (Varahram et al., 2014) primarily due to the effect on outward appearance as it mainly involve the skin. Individuals with psoriasis are also at increased risk of developing other chronic and serious medical conditions (co-morbidities) such as psoriatic arthritis, diabetes, cardiovascular disease and depression (Griffiths & Barker, 2007; Kupetsky & Keller, 2013).

According to World Health Organization, current prevalence of psoriasis affected population ranges between 0.09% and 11.4% (Michalek & Loring, 2016). In Malaysia, psoriasis accounts for 2-6% of yearly new attendees to the dermatology clinic (Huan, 2017). According to Malaysian Psoriasis Registry, from 23 participating dermatology centres, a total of 12,615 patients were notified in the registry from the period of October 2007 until December 2014 (National Dermatology Registry, 2014). From the recent numbers, majority of Malaysia patients with psoriasis are Malays (50.7%), followed by Chinese (21.8%), Indian (18.2%) and other ethnic groups (9.1%) (National Dermatology Registry, 2014). The largest number of patients reported to be over 18 years of age (93.7%) and categorized as adult with around 6.3% falls under paediatric population.

There are several types of psoriasis; the most common one is chronic plaque psoriasis or psoriasis vulgaris that affects about 85-90% of patients with the disease. This type usually present as localized or widespread elevated scaly plaques on surface of skin of elbows, knees, scalp and trunk. The other types are guttate psoriasis, flexural psoriasis, pustular psoriasis and erythroderma. Psoriasis can also be subdivided into Type 1 and Type 2 based on the bimodal distribution of age of the disease (Henseler & Christophers, 1985a). Type 1 psoriasis can be defined with early onset of disease (before and on 40 years of age), stronger family history, more severe disease and strong association with human leukocyte antigen Cw6 (HLA Cw6) (O'Brien et al., 2001; Rahman & Elder, 2005). Type 2 psoriasis has later onset (after 40 years of age) and more sporadic. The Malaysian Psoriasis Registry reported the largest amount of Malaysia adult psoriasis patients had age onset before 40 years old, in between 21-30 years old (National Dermatology Registry, 2014).

Psoriasis is a complex, multifactorial disease with no exact cause that is fully understood. Mainly, the disease manifestations involve interaction of genetic, environment and immunological factors that confers to individual susceptibility. The underlying immunological pathway that leads to psoriasis development involve several mechanisms that can be triggered or exacerbated by environmental factors such as stress, smoking, alcohol consumption and certain types of medication (Gerdes et al., 2010). These triggering factors will lead to the abnormal proliferation of keratinocytes that is common in psoriasis patients in which the growing rate is too fast compared to the normal skin growth (Gottlieb & Victor, 2002).

Underlying inflammatory pathway under the skin also shows abnormally increase expression of inflammatory cytokines (Bowcock, 1995; Liu et al., 2007; Ortonne, 1999) which is responsible for the disease pathology. These findings made it possible to develop treatment by targeting the specific cytokines involved in the psoriasis manifestations. However, developing the drugs does not stop the ongoing research of understanding psoriasis. Because of immune system roles, several genes that is involved in immune response have been identified to have an association with the disease; *IL12B* and *IL23R* (Capon et al., 2007; Cargill et al., 2007; Li et al., 2014; Nair et al., 2009; Tsoi et al., 2012). Therefore, polymorphisms in these genes also have possibility in altering the course of the disease.

Meanwhile, $1,25(OH)_2D_3$ and its analogs are also known as an effective topical psoriasis treatment. In the receptor of $1,25(OH)_2D_3$ lies several polymorphisms that has been associated with the risk of developing malignancies such as prostate cancer, breast cancer and malignant melanoma (Kostner et al., 2012). Because of the hyperactive proliferative properties of psoriasis, an association between vitamin D receptor (*VDR*) gene polymorphisms and risk of developing psoriasis is also possible.

1.2 Problem Statements

Psoriasis proved to be unique and perplexing disease. The disease manifestations involve uncontrolled and disordered skin growth and inflammation but do not seem to develop malignant potential. The lesions on the skin can be controlled and treated until the skin is apparently clear of the disease but the disease can recur and a cure has yet to be found. Several factors have been identified to trigger psoriasis development and they are also proven to exacerbate the severity along the course of the disease. Previous studies also showed that psoriasis can lead to the increase risk of metabolic syndrome (Armstrong et al., 2013; Chen et al., 2009; Voiculescu et al., 2014) and development of other medical conditions such as psoriatic arthritis, diabetes mellitus, hypertension, hyperlipidaemia and obesity. These conditions further increase the emotional stress on the patients and can further debilitate their conditions which usually lead to the shorter life span in psoriasis cases.

Treatment of psoriasis with 1,25(OH)2D3 which is an active form of vitamin D and its analogue have been proven to be safe and highly effective. Vitamin D inhibits epidermal proliferation and promotes epidermal differentiation. 1,25(OH)2D3 are also

reported to inhibits the activation of T-cells and induces the activation of CD25+/CD4+ regulatory T cells (van der Aar et al., 2011). However, clinical responses to this type of treatment are different among psoriasis patients and not all patients respond to treatment with vitamin D analogs (MacLaughlin et al., 1985; Smith et al., 1988). Previous studies have reported association exist between VDR genotypes and psoriasis breakouts, and also with treatment response to vitamin D analogs (Park et al., 1999).

Meanwhile, studies reported that genomic regulation of inflammatory cytokines such as IL-12 and IL-23 plays an important role in pathogenesis of the disease. Following this revelation, treatment with monoclonal antibodies agents against these cytokines prove to be a highly effective therapeutic in clinical settings for many psoriasis patients. By analysing the individual genotypes of VDR, IL12B and IL23R polymorphisms, we might be able to further investigate if polymorphisms on these genes confer risks to the development of psoriasis or predict the treatment outcome of this disease.

1.3 Significance of the Study

The aim of this study is to explore the genetic etiology of chronic plaque psoriasis in Malaysian population by investigating the association of specific genes with variants that confers risks to development of the disease. Similar studies have been reported in European and few Asian countries but so far none has been reported for Malaysian population. Therefore, by investigating specific gene polymorphism and identify the association with the disease might help us in the role of understanding such complex disease and if there are any identifiable risks in Malaysian population specifically.

1.4 Research Hypothesis

Vitamin D Receptor and cytokines (*IL12B* and *IL23R*) genes polymorphisms presenting risks for chronic plaque psoriasis in Malaysian populations.

1.5 Objectives

1.5.1 Main objective

To conduct a molecular epidemiological study to determine the effect of single nucleotide polymorphisms of *VDR*, *IL12B* and *IL23R* genes on risk of chronic plaque psoriasis patients attending Hospital Serdang Selangor, Malaysia.

1.5.2 Specific objectives

1. To determine:
   i. genotypes of Vitamin D-receptor (*VDR*), *IL12B* and *IL23R* genes
   ii. PASI (Psoriasis Area Severity Index) score, and medical history (site of initial appearance, precipitating factors, medication) , area of involvement (nail, joint, scalp), therapy status and response to therapy
   iii. socioeconomic background
   iv. family history
   v. lifestyle factors (smoking, alcohol).
   vi. BMI
2. To determine if Vitamin D-receptor (VDR), IL-12 and IL-23 gene polymorphisms are associated with risk of chronic plaque psoriasis, controlling for socioeconomic background, family history, lifestyle factors (smoking, alcohol) and BMI.
3. To determine if interaction exists between the factors in 1 (i) – (v) and SNPs of *VDR*, *IL12B* and *IL23R* genes and risk of chronic plaque psoriasis.

REFERENCES

Acikbas, I., Sanli, B., Tepeli, E., Ergin, S., Aktan, S., & Bagci, H. (2012). Vitamin D receptor gene polymorphisms and haplotypes (Apa I, Bsm I, Fok I, Taq I) in Turkish psoriasis patients. *Med Sci Monit,* ***18***(11), CR661-666.

Adam, B.A. (1980). Psoriasis in hospital population. *Med J Malaysia,* ***34***(4), 370-374.

Aggarwal, S., Ghilardi, N., Xie, M.H., De Sauvage, F.J., & Gurney, A.L. (2003). Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J Biol Chem,* ***278***(3), 1910-1914.

Aoki, T., & Yoshikawa, K. (1971). Psoriasis in Japan. *Arch Dermatol,* ***104***(3), 328-329.

Armstrong, A.W., Harskamp, C.T., & Armstrong, E.J. (2013). Psoriasis and metabolic syndrome: A systematic review and meta-analysis of observational studies. *Journal of the American Academy of Dermatology,* ***68***(4), 654-662.

Baeta, I.G.R., Bittencourt, F.V., Gontijo, B., & Goulart, E.M.A. (2014). Comorbidities and cardiovascular risk factors in patients with psoriasis. *Anais Brasileiros de Dermatologia,* ***89***(5), 735-744.

Baker, B.S., Ovigne, J.M., Powles, A.V., Corcoran, S., & Fry, L. (2003). Normal keratinocytes express Toll-like receptors (TLRs) 1, 2 and 5: modulation of TLR expression in chronic plaque psoriasis. *British Journal of Dermatology,* ***148***(4), 670-679.

Balendran, N., Clough, R.L., Arguello, J.R., Barber, R., Veal, C., Jones, A.B., Rosbotham, J.L., Little, A.M., Madrigal, A., Barker, J.N., Powis, S.H., & Trembath, R.C. (1999). Characterization of the major susceptibility region for psoriasis at chromosome 6p21.3. *J Invest Dermatol,* ***113***(3), 322-328.

Begon, E., Michel, L., Flageul, B., Beaudoin, I., Jean-Louis, F., Bachelez, H., Dubertret, L., & Musette, P. (2007). Expression, subcellular localization and cytokinic modulation of Toll-like receptors (TLRs) in normal human keratinocytes: TLR2 up-regulation in psoriatic skin. *Eur J Dermatol,* ***17***(6), 497-506.

Beutner, E., Jarzabek-Chorzelska, M., Jablonska, S., Chorzelski, T., & Rzęsa, G. (1978). Autoimmunity in psoriasis. *Arch Dermatol Res,* ***261***(2), 123-134.

Bornman, L., Campbell, S.J., Fielding, K., Bah, B., Jackson, S., Gustafson, P., Manneh, K., Lisse, I., Allen, A., Sirugo, G., Sylla, A., Aaby, P., Mcadam, K.P.W.J., Bah-Sow, O., Bennett, S., Lienhardt, C., & Hill, A.V.S. (2004). Vitamin D Receptor Polymorphisms and Susceptibility to Tuberculosis in West Africa: A Case-Control and Family Study. *The Journal of Infectious Diseases,* ***190***(9), 1631-1641.

Bos, J.D., & De Rie, M.A. (1999). The pathogenesis of psoriasis: immunological facts and speculations. *Immunol Today,* ***20***(1), 40-46.

Bos, J.D., Hulsebosch, H.J., Krieg, S.R., Bakker, P.M., & Cormane, R.H. (1983). Immunocompetent cells in psoriasis. In situ immunophenotyping by monoclonal antibodies. *Arch Dermatol Res,* ***275***(3), 181-189.

Bowcock, A.M. (1995). Genetic locus for psoriasis identified. *Ann Med,* ***27***(2), 183-186.

Bowcock, A.M., & Cookson, W.O. (2004). The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet,* ***13 Spec No 1***, R43-55.

Brandrup, F., Holm, N., Grunnet, N., Henningsen, K., & Hansen, H.E. (1982). Psoriasis in monozygotic twins: variations in expression in individuals with identical genetic constitution. *Acta Derm Venereol,* ***62***(3), 229-236.

Büchau, A.S., & Gallo, R.L. (2007). Innate Immunity and antimicrobial defense systems in psoriasis. *Clinics in Dermatology,* ***25***(6), 616-624. doi: 10.1016/j.clindermatol.2007.08.016

Capon, F., Meglio, P., Szaub, J., Prescott, N., Dunster, C., Baumber, L., Timms, K., Gutin, A., Abkevic, V., Burden, A.D., Lanchbury, J., Barker, J., Trembath, R., & Nestle, F. (2007). Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. *Human Genetics,* ***122***(2), 201-206.

Capon, F., Munro, M., Barker, J., & Trembath, R. (2002). Searching for the major histocompatibility complex psoriasis susceptibility gene. *J Invest Dermatol,* ***118***(5), 745-751.

Cargill, M., Schrodi, S.J., Chang, M., Garcia, V.E., Brandon, R., Callis, K.P., Matsunami, N., Ardlie, K.G., Civello, D., Catanese, J.J., Leong, D.U., Panko, J.M., Mcallister, L.B., Hansen, C.B., Papenfuss, J., Prescott, S.M., White, T.J., Leppert, M.F., Krueger, G.G., & Begovich, A.B. (2007). A Large-Scale Genetic Association Study Confirms IL12B and Leads to the Identification of IL23R as Psoriasis-Risk Genes. *American journal of human genetics,* ***80***(2), 273-290.

Chen, Y.-J., Shen, J.-L., Wu, C.-Y., Chang, Y.-T., Chen, C.-M., & Lee, F.-Y. (2009). Elevated plasma osteopontin level is associated with occurrence of psoriasis and is an unfavorable cardiovascular risk factor in patients with psoriasis. *Journal of the American Academy of Dermatology,* ***60***(2), 225-230.

Curry, J.L., Qin, J.-Z., Bonish, B., Carrick, R., Bacon, P., Panella, J., Robinson, J., & Nickoloff, B.J. (2003). Innate Immune-Related Receptors in Normal and Psoriatic Skin. *Archives of Pathology & Laboratory Medicine,* ***127***(2), 178-186.

Das, R.P., Jain, A.K., & Ramesh, V. (2009). Current concepts in the pathogenesis of psoriasis. *Indian J Dermatol,* ***54***(1), 7-12.

De Oliveira, M.D.F.S.P., Rocha, B.D.O., & Duarte, G.V. (2015). Psoriasis: classical and emerging comorbidities(). *Anais Brasileiros de Dermatologia,* ***90***(1), 9-20.

Denzer, N., Vogt, T., & Reichrath, J. (2011). Vitamin D receptor (VDR) polymorphisms and skin cancer: A systematic review. *Dermato-endocrinology,* ***3***(3), 205-210.

Duerr, R.H., Taylor, K.D., Brant, S.R., Rioux, J.D., Silverberg, M.S., Daly, M.J., Steinhart, A.H., Abraham, C., Regueiro, M., Griffiths, A., Dassopoulos, T., Bitton, A., Yang, H., Targan, S., Datta, L.W., Kistner, E.O., Schumm, L.P., Lee, A.T., Gregersen, P.K., Barmada, M.M., Rotter, J.I., Nicolae, D.L., & Cho, J.H. (2006). A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science,* ***314***(5804), 1461-1463.

Duffy, D.L., Spelman, L.S., & Martin, N.G. (1993). Psoriasis in Australian twins. *J Am Acad Dermatol,* ***29***(3), 428-434.

Ekburanawat, W., Ekpanyaskul, C., Brennan, P., Kanka, C., Tepsuwan, K., Temiyastith, S., Klinvimol, T., Pongnikorn, S., & Sangrajrang, S. (2010). Evaluation of non-viral risk factors for nasopharyngeal carcinoma in Thailand: results from a case-control study. *Asian Pac J Cancer Prev,* ***11***(4), 929-932.

Farber, E.M., Nall, M.L., & Watson, W. (1974). Natural history of psoriasis in 61 twin pairs. *Arch Dermatol,* ***109***(2), 207-211.

Filer, C., Ho, P., Smith, R.L., Griffiths, C., Young, H.S., Worthington, J., Bruce, I.N., & Barton, A. (2008). Investigation of association of the IL12B and IL23R genes with psoriatic arthritis. *Arthritis Rheum,* ***58***(12), 3705-3709.

Finlay, A.Y., & Khan, G.K. (1994). Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol,* ***19***(3), 210-216.

Fitch, E., Harper, E., Skorcheva, I., Kurtz, S.E., & Blauvelt, A. (2007). Pathophysiology of Psoriasis: Recent Advances on IL-23 and Th17 Cytokines. *Current rheumatology reports,* ***9***(6), 461-467.

Galimova, E.S., Akhmetova, V.L., & Khusnutdinova, E.K. (2008). Molecular genetic basis of susceptibility to psoriasis. *Russian Journal of Genetics,* ***44***(5), 513-522.

Gandhi, M., Alwawi, E., & Gordon, K.B. (2010). Anti-p40 antibodies ustekinumab and briakinumab: blockade of interleukin-12 and interleukin-23 in the treatment of psoriasis. *Semin Cutan Med Surg,* ***29***(1), 48-52.

Gerdes, S., Zahl, V.A., Weichenthal, M., & Mrowietz, U. (2010). Smoking and Alcohol Intake in Severely Affected Patients with Psoriasis in Germany. *Dermatology,* ***220***(1), 38-43.

Gibson, S. (2005). *Principles of Nutritional Assessment* (2nd ed.). New York: Oxford University Press.

Gordon, K.B., Papp, K.A., Hamilton, T.K., Walicke, P.A., Dummer, W., Li, N., Bresnahan, B.W., & Menter, A. (2003). Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA,* ***290***(23), 3073-3080.

Gottlieb, A.B. (2003). Infliximab for psoriasis. *J Am Acad Dermatol,* ***49***(2 Suppl), S112-117.

Gottlieb, A.B., & Victor, F.C. (2002). TNF-alpha and apoptosis: implications for the pathogenesis and treatment of psoriasis. [Article]. *Journal of Drugs in Dermatology,* ***1***, 264+.

Griffiths, C.E., & Barker, J.N. (2007). Pathogenesis and clinical features of psoriasis. *Lancet,* ***370***(9583), 263-271.

Grjibovski, A.M., Olsen, A.O., Magnus, P., & Harris, J.R. (2007). Psoriasis in Norwegian twins: contribution of genetic and environmental effects. *J Eur Acad Dermatol Venereol,* ***21***(10), 1337-1343.

Guilhou, J.J., Meynadier, J., & Clot, J. (1978). New concepts in the pathogenesis of psoriasis. *British Journal of Dermatology,* ***98***(5), 585-592.

Gupta, M.A., Schork, N.J., Gupta, A.K., Kirkby, S., & Ellis, C.N. (1993). Suicidal ideation in psoriasis. *International Journal of Dermatology,* ***32***(3), 188-190.

Hajeer, A.H., & Hutchinson, I.V. (2000). TNF-alpha gene polymorphism: clinical and biological implications. *Microsc Res Tech,* ***50***(3), 216-228.

Hardy-Weinberg equilibrium. (2014). Retrieved from Scitable by Nature Education http://www.nature.com/scitable/definition/hardy-weinberg-equilibrium-122

Henseler, T., & Christophers, E. (1985a). Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol,* ***13***(3), 450-456.

Henseler, T., & Christophers, E. (1985b). Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. *Journal of the American Academy of Dermatology,* ***13***(3), 450-456.

Hirschhorn, J.N., Lohmueller, K., Byrne, E., & Hirschhorn, K. (2002). A comprehensive review of genetic association studies. *Genet Med,* ***4***(2), 45-61.

Huan, K.Y. (2017). Psoriasis. Retrieved from http://www.dermatology.org.my/pdf/Psoriasis%20English%20Dr%20Khor%20YH%20Edit.pdf

Huffmeier, U., Lascorz, J., Bohm, B., Lohmann, J., Wendler, J., Mossner, R., Reich, K., Traupe, H., Kurrat, W., Burkhardt, H., & Reis, A. (2009). Genetic variants of

the IL-23R pathway: association with psoriatic arthritis and psoriasis vulgaris, but no specific risk factor for arthritis. *J Invest Dermatol,* ***129***(2), 355-358.

Jurutka, P.W., Whitfield, G.K., Hsieh, J.C., Thompson, P.D., Haussler, C.A., & Haussler, M.R. (2001). Molecular nature of the vitamin D receptor and its role in regulation of gene expression. *Rev Endocr Metab Disord,* ***2***(2), 203-216.

Kelsey, J.L., Whittemore, A.S., Evans, A.S., & Thompson, W.D. (1996). *Methods in Observational Epidemiology*: Oxford University Press.

Kostner, K., Denzer, N., Koreng, M., Reichrath, S., Graber, S., Klein, R., Tilgen, W., Vogt, T., & Reichrath, J. (2012). Association of genetic variants of the vitamin D receptor (VDR) with cutaneous squamous cell carcinomas (SCC) and basal cell carcinomas (BCC): a pilot study in a German population. *Anticancer Res,* ***32***(1), 327-333.

Krueger, G., Koo, J., Lebwohl, M., Menter, A., Stern, R.S., & Rolstad, T. (2001). The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol,* ***137***(3), 280-284.

Krueger, G.G., & Callis, K.P. (2003). Development and use of alefacept to treat psoriasis. *Journal of the American Academy of Dermatology,* ***49***(2, Supplement), 87-97.

Kupetsky, E.A., & Keller, M. (2013). Psoriasis Vulgaris: An Evidence-Based Guide for Primary Care. *The Journal of the American Board of Family Medicine,* ***26***(6), 787-801.

Langley, R.G.B., Krueger, G.G., & Griffiths, C.E.M. (2005). Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the Rheumatic Diseases,* ***64***(suppl 2), ii18-ii23.

Lankford, C.S., & Frucht, D.M. (2003). A unique role for IL-23 in promoting cellular immunity. *J Leukoc Biol,* ***73***(1), 49-56.

Leibundgut-Landmann, S., Grosz, O., Robinson, M.J., Osorio, F., Slack, E.C., Tsoni, S.V., Schweighoffer, E., Tybulewicz, V., Brown, G.D., Ruland, J., & Reis E Sousa, C. (2007). Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. [10.1038/ni1460]. *Nat Immunol,* ***8***(6), 630-638.

Li, J., Zhang, C., Wang, J.B., Chen, S.S., Zhang, T.P., Li, S., Pan, H.F., & Ye, D.Q. (2016). Relationship between the IL12B (rs3212227) gene polymorphism and susceptibility to multiple autoimmune diseases: A meta-analysis. *Mod Rheumatol,* ***26***(5), 749-756.

Li, X., Bai, L., Fang, J., Hou, S., Zhou, Q., Yu, H., Kijlstra, A., & Yang, P. (2014). Genetic variations of IL-12B, IL-12Rbeta1, IL-12Rbeta2 in Behcet's disease and VKH syndrome. *PLoS One,* ***9***(5), e98373.

Liu, Y., Helms, C., Liao, W., Zaba, L.C., Duan, S., Gardner, J., Wise, C., Miner, A., Malloy, M.J., Pullinger, C.R., Kane, J.P., Saccone, S., Worthington, J., Bruce, I., Kwok, P.Y., Menter, A., Krueger, J., Barton, A., Saccone, N.L., & Bowcock, A.M. (2008). A Genome-Wide Association Study of Psoriasis and Psoriatic Arthritis Identifies New Disease Loci. *PLoS Genetics,* ***4***(4), e1000041.

Liu, Y., Krueger, J.G., & Bowcock, A.M. (2007). Psoriasis: genetic associations and immune system changes. *Genes Immun,* ***8***(1), 1-12.

Lonnberg, A.S., Skov, L., Skytthe, A., Kyvik, K.O., Pedersen, O.B., & Thomsen, S.F. (2013). Heritability of psoriasis in a large twin sample. *Br J Dermatol,* ***169***(2), 412-416.

Lonnberg, A.S., Skov, L., Skytthe, A., Kyvik, K.O., Pedersen, O.B., & Thomsen, S.F. (2016). Smoking and risk for psoriasis: a population-based twin study. *Int J Dermatol,* ***55***(2), e72-78.

Maclaughlin, J.A., Gange, W., Taylor, D., Smith, E., & Holick, M.F. (1985). Cultured psoriatic fibroblasts from involved and uninvolved sites have a partial but not absolute resistance to the proliferation-inhibition activity of 1,25-dihydroxyvitamin D3. *Proc Natl Acad Sci U S A,* ***82***(16), 5409-5412.

Martin, D.A., Towne, J.E., Kricorian, G., Klekotka, P., Gudjonsson, J.E., Krueger, J.G., & Russell, C.B. (2013). The emerging Role of Interleukin-17 in the Pathogenesis of Psoriasis: Preclinical and Clinical Findings. *The Journal of Investigative Dermatology,* ***133***(1), 17-26.

Medzhitov, R., & Janeway, C.A., Jr. (1997). Innate Immunity: The Virtues of a Nonclonal System of Recognition. *Cell,* ***91***(3), 295-298.

Michalek, I.M., & Loring, B. (2016). Global report on psoriasis Retrieved from http://apps.who.int/iris/bitstream/10665/204417/1/9789241565189_eng.pdf

Morar, N., Willis-Owen, S.A., Maurer, T., & Bunker, C.B. (2010). HIV-associated psoriasis: pathogenesis, clinical features, and management. *The Lancet Infectious Diseases,* ***10***(7), 470-478.

Nair, R.P., Duffin, K.C., Helms, C., Ding, J., Stuart, P.E., Goldgar, D., Gudjonsson, J.E., Li, Y., Tejasvi, T., Feng, B.J., Ruether, A., Schreiber, S., Weichenthal, M., Gladman, D., Rahman, P., Schrodi, S.J., Prahalad, S., Guthery, S.L., Fischer, J., Liao, W., Kwok, P.Y., Menter, A., Lathrop, G.M., Wise, C.A., Begovich, A.B., Voorhees, J.J., Elder, J.T., Krueger, G.G., Bowcock, A.M., & Abecasis, G.R. (2009). Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet,* ***41***(2), 199-204.

Nair, R.P., Stuart, P., Henseler, T., Jenisch, S., Chia, N.V., Westphal, E., Schork, N.J., Kim, J., Lim, H.W., Christophers, E., Voorhees, J.J., & Elder, J.T. (2000). Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. *Am J Hum Genet,* ***66***(6), 1833-1844.

Nair, R.P., Stuart, P.E., Kullavanijaya, P., Tejasvi, T., Voorhees, J.J., & Elder, J.T. (2010). Genetic evidence for involvement of the IL23 pathway in Thai psoriatics. *Archives of Dermatological Research,* ***302***(2), 139-143.

Naldi, L., Chatenoud, L., Linder, D., Belloni Fortina, A., Peserico, A., Virgili, A.R., Bruni, P.L., Ingordo, V., Lo Scocco, G., Solaroli, C., Schena, D., Barba, A., Di Landro, A., Pezzarossa, E., Arcangeli, F., Gianni, C., Betti, R., Carli, P., Farris, A., Barabino, G.F., & La Vecchia, C. (2005). Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *J Invest Dermatol,* ***125***(1), 61-67.

National Dermatology Registry. (2014). 2007-2014 annual report of the Malaysian Psoriasis Registry, Retrieved from http://www.arcm.org.my/dermreg/documents/Annual_Report_2007_2014_pdf.

O'brien, K.P., Holm, S.J., Nilsson, S., Carlen, L., Rosenmuller, T., Enerback, C., Inerot, A., & Stahle-Backdahl, M. (2001). The HCR gene on 6p21 is unlikely to be a psoriasis susceptibility gene. *J Invest Dermatol,* ***116***(5), 750-754.

Okita, H., Ohtsuka, T., Yamakage, A., & Yamazaki, S. (2002). Polymorphism of the vitamin D3 receptor in patients with psoriasis. *Archives of Dermatological Research,* ***294***(4), 159-162.

Oppmann, B., Lesley, R., Blom, B., Timans, J.C., Xu, Y., Hunte, B., Vega, F., Yu, N., Wang, J., Singh, K., Zonin, F., Vaisberg, E., Churakova, T., Liu, M., Gorman, D., Wagner, J., Zurawski, S., Liu, Y., Abrams, J.S., Moore, K.W., Rennick, D., De Waal-Malefyt, R., Hannum, C., Bazan, J.F., & Kastelein, R.A. (2000).

Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity,* ***13***(5), 715-725.

Ortonne, J.P. (1999). Recent developments in the understanding of the pathogenesis of psoriasis. *Br J Dermatol,* ***140 Suppl 54***, 1-7.

Park, B.-S., Lee, D.-Y., Youn, J.-I., Park, J.-S., & Kim, I.-G. (1999). Vitamin D Receptor Polymorphism is Associated with Psoriasis. *Journal of Investigative Dermatology,* ***112***(1), 113-116.

Rahman, P., & Elder, J.T. (2005). Genetic epidemiology of psoriasis and psoriatic arthritis. *Annals of the Rheumatic Diseases,* ***64***(suppl 2), ii37-ii39. doi: 10.1136/ard.2004.030775

Reveille, J.D., Sims, A.-M., Danoy, P., Evans, D.M., Leo, P., Pointon, J.J., Jin, R., Zhou, X., Bradbury, L.A., Appleton, L.H., Davis, J.C., Diekman, L., Doan, T., Dowling, A., Duan, R., Duncan, E.L., Farrar, C., Hadler, J., Harvey, D., Karaderi, T., Mogg, R., Pomeroy, E., Pryce, K., Taylor, J., Savage, L., Deloukas, P., Kumanduri, V., Peltonen, L., Ring, S.M., Whittaker, P., Glazov, E., Thomas, G.P., Maksymowych, W.P., Inman, R.D., Ward, M.M., Stone, M.A., Weisman, M.H., Wordsworth, B.P., & Brown, M.A. (2010). Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. *Nature genetics,* ***42***(2), 123-127.

Revicki, D.A., Willian, M.K., Menter, A., Saurat, J.H., Harnam, N., & Kaul, M. (2008). Relationship between Clinical Response to Therapy and Health-Related Quality of Life Outcomes in Patients with Moderate to Severe Plaque Psoriasis. *Dermatology,* ***216***(3), 260-270.

Richards, H.L., Fortune, D.G., Griffiths, C.E.M., & Main, C.J. (2001). The contribution of perceptions of stigmatisation to disability in patients with psoriasis. *Journal of Psychosomatic Research,* ***50***(1), 11-15.

Smith, E.L., Pincus, S.H., Donovan, L., & Holick, M.F. (1988). A novel approach for the evaluation and treatment of psoriasis: Oral or topical use of 1,25-dihydroxyvitamin D3 can be a safe and effective therapy for psoriasis. *Journal of the American Academy of Dermatology,* ***19***(3), 516-528.

Smith, E.L., Walworth, N.C., & Holick, M.F. (1986a). Effect of 1 alpha,25-dihydroxyvitamin D3 on the morphologic and biochemical differentiation of cultured human epidermal keratinocytes grown in serum-free conditions. *J Invest Dermatol,* ***86***(6), 709-714.

Smith, E.L., Walworth, N.D., & Holick, M.F. (1986b). Effect of 1,25-dihydroxyvitamin D3 on the morphologic and biochemical differentiation of cultured human epidermal keratinocytes grown in serum-free conditions. *J Invest Dermatol,* ***86***, 709-714.

Smith, R.L., Warren, R.B., Eyre, S., Ho, P., Ke, X., Young, H.S., Griffiths, C.E., & Worthington, J. (2008). Polymorphisms in the IL-12beta and IL-23R genes are associated with psoriasis of early onset in a UK cohort. *J Invest Dermatol,* ***128***(5), 1325-1327.

Stark, M.A., Huo, Y., Burcin, T.L., Morris, M.A., Olson, T.S., & Ley, K. (2005). Phagocytosis of Apoptotic Neutrophils Regulates Granulopoiesis via IL-23 and IL-17. *Immunity,* ***22***(3), 285-294.

Su, D., Ma, S., Liu, P., Jiang, Z., Lv, W., Zhang, Y., Deng, Q., Smith, S., & Yu, H. (2007). Genetic polymorphisms and treatment response in advanced non-small cell lung cancer. *Lung Cancer,* ***56***(2), 281-288.

Tan, E.S., Chong, W.S., & Tey, H.L. (2012). Nail psoriasis: a review. *Am J Clin Dermatol,* ***13***(6), 375-388.

Trembath, R.C., Clough, R.L., Rosbotham, J.L., Jones, A.B., Camp, R.D., Frodsham, A., Browne, J., Barber, R., Terwilliger, J., Lathrop, G.M., & Barker, J.N. (1997). Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet,* ***6***(5), 813-820.

Tsoi, L.C., Spain, S.L., Knight, J., Ellinghaus, E., Stuart, P.E., Capon, F., Ding, J., Li, Y., Tejasvi, T., Gudjonsson, J.E., Kang, H.M., Allen, M.H., Mcmanus, R., Novelli, G., Samuelsson, L., Schalkwijk, J., Stahle, M., Burden, A.D., Smith, C.H., Cork, M.J., Estivill, X., Bowcock, A.M., Krueger, G.G., Weger, W., Worthington, J., Tazi-Ahnini, R., Nestle, F.O., Hayday, A., Hoffmann, P., Winkelmann, J., Wijmenga, C., Langford, C., Edkins, S., Andrews, R., Blackburn, H., Strange, A., Band, G., Pearson, R.D., Vukcevic, D., Spencer, C.C.A., Deloukas, P., Mrowietz, U., Schreiber, S., Weidinger, S., Koks, S., Kingo, K., Esko, T., Metspalu, A., Lim, H.W., Voorhees, J.J., Weichenthal, M., Wichmann, H.E., Chandran, V., Rosen, C.F., Rahman, P., Gladman, D.D., Griffiths, C.E.M., Reis, A., Kere, J., Nair, R.P., Franke, A., Barker, J.N.W.N., Abecasis, G.R., Elder, J.T., & Trembath, R.C. (2012). Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet,* ***44***(12), 1341-1348.

Tsunemi, Y., Saeki, H., Nakamura, K., Sekiya, T., Hirai, K., Fujita, H., Asano, N., Kishimoto, M., Tanida, Y., Kakinuma, T., Mitsui, H., Tada, Y., Wakugawa, M., Torii, H., Komine, M., Asahina, A., & Tamaki, K. (2002). Interleukin-12 p40 gene (IL12B) 3′-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. *J Dermatol Sci,* ***30***(2), 161-166.

Uitterlinden, A.G., Fang, Y., Van Meurs, J.B., Pols, H.A., & Van Leeuwen, J.P. (2004). Genetics and biology of vitamin D receptor polymorphisms. *Gene,* ***338***(2), 143-156.

Van Der Aar, A.M., Sibiryak, D.S., Bakdash, G., Van Capel, T.M., Van Der Kleij, H.P., Opstelten, D.J., Teunissen, M.B., Kapsenberg, M.L., & De Jong, E.C. (2011). Vitamin D3 targets epidermal and dermal dendritic cells for induction of distinct regulatory T cells. *J Allergy Clin Immunol,* ***127***(6), 1532-1540 e1537.

Varahram, M., Farnia, P., Nasiri, M.J., Afraei Karahrudi, M., Kazampour, M., & Velayati, A.A. (2014). Association of mycobacterium tuberculosis lineages with IFN-Γ and TNF-A gene polymorphisms among pulmonary tuberculosis patient. *2014,* ***6***(1).

Voiculescu, V.M., Lupu, M., Papagheorghe, L., Giurcaneanu, C., & Micu, E. (2014). Psoriasis and Metabolic Syndrome – scientific evidence and therapeutic implications. *Journal of Medicine and Life,* ***7***(4), 468-471.

Wong, R.H., Wei, J.C., Huang, C.H., Lee, H.S., Chiou, S.Y., Lin, S.H., Cai, Y.W., Hung, P.H., Wang, M.F., & Yang, S.F. (2012). Association of IL-12B genetic polymorphism with the susceptibility and disease severity of ankylosing spondylitis. *J Rheumatol,* ***39***(1), 135-140.

Wuepper, K.D., Coulter, S.N., & Haberman, A. (1990). Psoriasis vulgaris: a genetic approach. *J Invest Dermatol,* ***95***(5), 2S-4S.

Yannam, G.R., Gutti, T., & Poluektova, L.Y. (2012). IL-23 in Infections, Inflammation, Autoimmunity and Cancer: Possible Role in HIV-1 and AIDS. *Journal of Neuroimmune Pharmacology,* ***7***(1), 95-112.

Zhu, K.J., Zhu, C.Y., Shi, G., & Fan, Y.M. (2013). Meta-analysis of IL12B polymorphisms (rs3212227, rs6887695) with psoriasis and psoriatic arthritis. *Rheumatol Int,* ***33***(7), 1785-1790.

Zuel-Fakkar, N.M., Kamel, M.M., Asaad, M.K., Mahran, M.Z., & Shehab, A.A. (2011). A study of ApaI and TaqI genotypes of the vitamin D receptor in Egyptian patients with psoriasis. *Clinical and Experimental Dermatology,* ***36***(4), 355-359.