Article

Impact of ABCG2 Gene Polymorphism on the Predisposition to Psoriasis

Yu-Huei Huang1,2,3, Lai-Chu See4,5,6,*, Ya-Ching Chang2,3, Wen-Hung Chung2,3,7, Lun-Ching Chang8,*, Shun-Fa Yang1,9,* and Shih-Chi Su7,*

1 Institute of Medicine, Chung Shan Medical University, Taichung 402, Taiwan; huangyh@cloud.cgmh.org.tw
2 Department of Dermatology, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan 333, Taiwan; yychang@cgmh.org.tw (Y.-C.C.); chung1@cgmh.org.tw (W.-H.C.)
3 School of Medicine, College of Medicine, Chang Gung University, Taoyuan 333, Taiwan
4 Department of Public Health, Chang Gung University, Taoyuan 333, Taiwan; lichu@mail.cgu.edu.tw
5 Biostatistics Core Laboratory, Molecular Medicine Research Center, Chang Gung University, Taoyuan 333, Taiwan
6 Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan 333, Taiwan
7 Whole-Genome Research Core Laboratory of Human Diseases, Chang Gung Memorial Hospital, Keelung 204, Taiwan
8 Department of Mathematical Sciences, Florida Atlantic University, Boca Raton, FL 33431, USA; changl@fau.edu
9 Department of Medical Research, Chung Shan Medical University Hospital, Taichung 402, Taiwan
* Correspondence: ysf@csmu.edu.tw (S.-F.Y.); ssu1@cgmh.org.tw (S.-C.S.); Tel.: +886-2-24329292-3388

Abstract: Psoriasis is a chronic inflammatory disease which is caused by the interaction between genetic and environmental factors. Evidence shows an association of psoriasis with co-morbidities including cardiovascular diseases, metabolic syndrome and hyperuricemia. Genome-wide association studies have revealed that the ABCG2 gene encoding ATP-binding cassette G2 protein was associated with inflammation and higher serum urate concentrations. In this study, we aimed to evaluate the role of ABCG2 gene polymorphisms on the susceptibility to psoriasis. The genotype distribution of two ABCG2 single nucleotide polymorphisms (SNPs), rs2231142 and rs2231137, was examined in 410 psoriasis patients and 1,089 gender-matched non-psoriasis controls. We found that heterozygotes (GT) for rs2231142 were associated with a decreased risk of psoriasis (p = 0.001; adjusted OR = 0.532; 95% CI, 0.370–0.765) after adjusting for age, as compared with homozygotes for the major allele (GG). Subjects who carried at least one polymorphic allele (homozygote or heterozygote for the minor allele) were less susceptible to psoriasis (p = 0.002; adjusted OR = 0.594; 95% CI, 0.249–0.823) and bearing higher serum urate levels (p = 0.026) than those homozygous for the major allele. Our results indicated that the ABCG2 gene polymorphism was associated with the risk of psoriasis.

Keywords: psoriasis; single nucleotide polymorphisms; ABCG2

1. Introduction

Psoriasis is an inflammatory and multifactorial disease, which is caused by the interaction between genetic and environmental factors[1,2]. Linkage studies have uncovered nine genomic regions, known as psoriasis susceptibility (PSORS) 1–9 which were supposed to contribute to disease susceptibility[3]. Recent advances in the genome-wide associated studies (GWAS) identified more than 40 psoriasis susceptibility loci. Proteins encoded by genes at these loci were linked to regulate the inflammatory pathways and skin barrier function involved in the development of psoriatic plaques[4]. Cytokine members of the IL-23/IL-17 family were known to be substantial in driving skin inflammation due to the success of IL-23- or IL-17-targeted biologics in treating psoriasis[5]. IL-23 expressed by dendritic cells is crucial for Th17 development and expansion. Th17-driven IL-17A...
and IL-22 act on keratinocytes to induce CC chemokine 20 and attract Th17 cells for further keratinocyte activation in a positive feedback manner [6]. These cytokine-signaling pathways were associated with several psoriasis susceptibility loci such as IL23A, IL23R, and NFKBIZ [7–9]. The findings of these risk alleles support a role of IL-23 and IL-17 in psoriasis pathogenesis.

The ABCG2 (ATH-binding cassette G2) protein, a half transporter, is one member of ABC (ATP-binding cassette) transporters that export multiple compounds, including lipids, amino acids, uric acid, inorganic ions, chemotherapeutics [10], and environmental and endogenous toxins [11,12] across membranes. ABC transporters were initially identified for their roles in the onset and maintenance of multidrug resistance. Several reports have shown their contributions to the development, differentiation, and maturation of immune cells and their involvement in migration of immune effector cells [13]. The presence of these transporters on immune cells could be implicated in the onset of autoimmune diseases by active secretion of inflammatory mediators such as prostaglandins, leukotrienes, and cyclic nucleotides (cAMP, cGMP) [14,15]. Numerous studies have demonstrated that ABCG2, expressed on hematopoietic stem cells, monocyte-derived dendritic cells, and Langerhans cells, has played an important role in their differentiation, maturation, and migration [16,17]. In inflammatory conditions, ABC transporters influence the susceptibility to development of rheumatoid arthritis [18,19] where marked expression of ABCG2 in the intimal lining layer and on macrophages in the synovial tissue were observed [20]. Increased expression of ABCG2 in peripheral blood mononuclear cells was described in psoriasis as well [21]. All these findings implicate ABCG2 as not only a drug efflux pump but a critical factor in inflammatory processes and autoimmune diseases.

Here, two commonly-studied missense polymorphisms (V12M; rs2231137 and Q141K; rs2231142) from the ABCG2 gene were selected on the basis of their potential involvement in the susceptibility of hyperuricemia for examining their association with psoriasis [12]. These two missense variants of the ABCG2 gene were shown to have significant impacts on ABCG2 characteristics, leading to reduced ABCG2 protein expression and dysfunction. [22,23]. ABCG2 genetic variants have been reported to have significant impacts on ABCG2 characteristics, leading to reduced ABCG2 protein expression and dysfunction [22,23]. ABCG2 genetic variants have been reported to be associated with reduced efficacy of drug treatments and risks of diseases, such as gout, Alzheimer’s disease, and isolated septal defects [24–27]. Therefore, the aim of this study was to test the hypothesis that ABCG2 genetic polymorphism may potentially confer the susceptibility to psoriasis. Through assessing the genotype distribution of two ABCG2 single nucleotide polymorphisms (SNPs), rs2231142 and rs2231137, in 410 psoriatic patients and 1089 controls, we demonstrated that ABCG2 gene polymorphism was associated with the predisposition to psoriasis.

2. Materials and Methods

2.1. Subjects

The study was comprised of 410 patients with psoriasis and 1089 gender-matched, psoriasis-free controls with the approval by the institutional review board of Chang Gung Medical Foundation, Taiwan (No. 201503178B0). The psoriasis patients were recruited in the Chang Gung Memorial Hospital from 2017 to 2019 and the control subjects were enrolled in the Chang Gung Memorial Hospital and selected from the Integrated Blood Bank of the Chang Gung University. Patients received physical examination and laboratory blood tests including uric acid, high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides upon recruitment. Psoriasis severity was measured by using the psoriasis area and severity index (PASI) score. Clinical information regarding age, gender, coexistence of psoriatic arthritis, and habits of smoking and alcohol drinking was collected.

2.2. Genotyping of ABCG2 SNPs

Genomic DNA was extracted from the whole blood with QIAamp DNA Blood Mini Kits (Qiagen, Santa Clarita, CA, USA), as described in detail previously [28]. DNA was dissolved in Tris-EDTA buffer and then quantified by a measurement of OD260. Analysis of
allelic discrimination for the two ABCG2 SNPs (rs2231142 and rs2231137) was performed by using the TaqMan assay with an ABI StepOne Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and then assessed with SDS 3.0 software (Applied Biosystems).

2.3. Statistical Analysis

The differences in demographic parameters between patients with psoriasis and controls were estimated by using the Mann-Whitney U test and Fisher’s exact test. Adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) for the association between genotype frequencies and the risk of psoriasis were calculated by multiple logistic regression models after controlling for other covariates. Data were analyzed with SAS 9.1 statistical software (SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered significant.

3. Results

3.1. Characterization of Study Participants

In this study, 410 psoriasis patients and 1089 gender-matched non-psoriatic controls were enrolled. Demographic and clinical characteristics are presented in Table 1. In addition to age, significant differences in several metabolism-related parameters such as body mass index, weight, and the levels of high-density lipoprotein, total cholesterol, and triglycerides were observed between two study cohorts.

Table 1. Distributions of demographic characteristics of 1089 control and 410 patients with psoriasis.

| Variable                | Control (n = 1089) | Patients (n = 410) | p Value |
|-------------------------|-------------------|-------------------|---------|
| Age (years)             | Mean ± S.D.       | Mean ± S.D.       | p < 0.001 |
|                         | 54.22 ± 11.09     | 41.40 ± 12.55     |         |
| Gender                  |                   |                   |         |
| Male                    | 765 (70.2%)       | 291 (71.0%)       | p = 0.783 |
| Female                  | 324 (29.8%)       | 119 (29.0%)       |         |
| Height (cm)             | 163.35 ± 8.16     | 167.26 ± 8.03     | p < 0.001 |
| Weight (kg)             | 68.99 ± 12.23     | 74.34 ± 15.69     | p < 0.001 |
| Body mass index (BMI)   | 25.79 ± 3.84      | 26.50 ± 4.93      | p = 0.004 |
| Uric acid (mg/dL)       | 6.22 ± 1.42       | 6.34 ± 1.65       | p = 0.161 |
| high-density lipoprotein (HDL, mg/dL) | 56.01 ± 14.82 | 47.42 ± 11.58 | p < 0.001 |
| low-density lipoprotein (LDL, mg/dL) | 117.32 ± 27.69 | 116.59 ± 35.99 | p = 0.825 |
| Total cholesterol (mg/dL) | 202.16 ± 37.30 | 192.43 ± 63.16 | p < 0.001 |
| Triglycerides (mg/dL)   | 151.86 ± 125.22   | 136.82 ± 145.77   | p = 0.048 |
| PASI score              |                   |                   |         |
| Onset (age, on skin)    |                   |                   |         |
| Arthritis pain          |                   |                   |         |
| No                      |                   |                   |         |
| Yes                     |                   |                   |         |

3.2. Association between ABCG2 Gene Polymorphisms and Psoriasis

To understand the possible association of ABCG2 gene polymorphisms with the risk of psoriasis, the genotype distributions of two SNPs, rs2231142 and rs2231137, were examined (Table 2). We observed that Heterozygous participants (GT) for rs2231142 were associated with a decreased risk of psoriasis (p = 0.001; adjusted OR = 0.532; 95% CI, 0.370–0.765) as compared to homozygotes for the major allele (GG) after adjusting for age. Furthermore, subjects who carried at least one polymorphic allele (homozygote or heterozygote for the minor allele, GT + TT) were less susceptible to psoriasis than those homozygous for the major allele (p = 0.002; adjusted OR = 0.594; 95% CI, 0.249–0.823). However, no significant association between psoriasis and rs2231137 was detected. These results indicate a protective impact of ABCG2 polymorphisms on psoriasis.
Table 2. Distribution of ABCG2 genotype frequencies in 1089 controls and 410 psoriasis patients.

| Variable          | Controls  | Patients | OR (95% CI) | AOR (95% CI) |
|-------------------|-----------|----------|-------------|--------------|
|                   | (n = 1089) | (n = 410) |             |              |
| ABCG2 rs2231142   |           |          |             |              |
| GG                | 523 (48.0%) | 234 (57.1%) | 1.00        | 1.00         |
| GT                | 445 (40.9%) | 137 (33.4%) | 0.688 (0.538–0.880) | 0.532 (0.370–0.765) |
| TT                | 121 (11.1%) | 39 (9.5%) | 0.720 (0.487–1.067) | 0.812 (0.485–1.358) |
| GT + TT           | 566 (52.0%) | 176 (42.9%) | 0.695 (0.553–0.874) | 0.594 (0.429–0.823) |
| ABCG2 rs2231137   |           |          |             |              |
| CC                | 486 (44.6%) | 180 (43.9%) | 1.00        | 1.00         |
| CT                | 476 (43.7%) | 180 (43.9%) | 1.021 (0.801–1.301) | 0.928 (0.656–1.313) |
| TT                | 127 (11.7%) | 50 (12.2%) | 1.063 (0.735–1.538) | 1.124 (0.681–1.856) |
| CT + TT           | 603 (55.4%) | 230 (56.1%) | 1.030 (0.819–1.295) | 0.943 (0.665–1.337) |

The odds ratio (OR) with 95% confidence intervals (CIs) were estimated by logistic regression models. The adjusted OR (AOR) with their 95% CIs was estimated by multiple logistic regression models after controlling for age.

3.3. Interaction of ABCG2 Gene Polymorphisms with Clinical Characteristics among Patients with Psoriasis

Since a genetic predisposition to psoriasis was noted, we further analyzed the effect of ABCG2 gene polymorphisms on clinical characteristics in patients with psoriasis (Tables 3 and 4). A significant association of rs2231142 variants (GG vs. GT + TT) with hyperuricemia (p = 0.026; OR = 1.608, 95% CI: 1.057–2.447) was observed in psoriasis patients. However, such association of rs2231142 variants was not demonstrated with age of onset, family history of psoriasis, baseline PASI score, or psoriatic arthritis.

Table 3. Distribution of ABCG2 rs2231142 genotype frequencies and the clinical status among 410 patients with psoriasis.

| Variable          | GG (%) | GT + TT (%) | OR (95% CI) | p Value |
|-------------------|--------|-------------|-------------|---------|
|                   | (n = 234) | (n = 176) |             |         |
| Uric acid #       |        |             |             |         |
| <7 mg/dL          | 170 (72.6%) | 109 (62.3%) | 1.00        |         |
| ≥7 mg/dL          | 64 (27.4%) | 66 (37.7%) | 1.608 (1.057–2.447) | 0.026   |
| Family History    |        |             |             |         |
| None              | 159 (67.9%) | 131 (74.4%) | 1.00        |         |
| Parent/Children   | 37 (15.8%) | 24 (13.6%) | 0.787 (0.448–1.383) | 0.405   |
| Others            | 38 (16.2%) | 21 (11.9%) | 0.671 (0.375–1.199) | 0.176   |
| PASI #            |        |             |             |         |
| <10               | 128 (54.9%) | 99 (56.3%) | 1.00        |         |
| ≥10               | 105 (45.1%) | 77 (43.7%) | 0.948 (0.639–1.406) | 0.791   |
| Onset (age, on skin) |        |             |             |         |
| <40               | 198 (84.6%) | 145 (82.4%) | 1.00        |         |
| ≥40               | 36 (15.4%) | 31 (17.6%) | 1.176 (0.695–1.989) | 0.546   |
| Arthritis pain    |        |             |             |         |
| No                | 150 (64.1%) | 125 (71.0%) | 1.00        |         |
| Yes               | 84 (35.9%) | 51 (29.0%) | 0.729 (0.478–1.110) | 0.140   |

*p = 409.*
Table 4. Distribution of ABCG2 rs2231137 genotype frequencies and the clinical status among 410 patients with psoriasis.

| Variable             | CC (%) (n = 180) | CT + TT (%) (n = 180) | OR (95% CI)       | p Value  |
|----------------------|------------------|-----------------------|-------------------|----------|
| Urinary acid #       |                  |                       |                   |          |
| <7 mg/dL             | 114 (63.7%)      | 124 (68.9%)           | 1.00              |          |
| ≥7 mg/dL             | 65 (36.3%)       | 56 (31.1%)            | 0.792 (0.511–1.228) | p = 0.297 |
| Family History       |                  |                       |                   |          |
| None                 | 132 (73.3%)      | 130 (72.2%)           | 1.00              |          |
| Parent/Children      | 21 (11.7%)       | 23 (12.8%)            | 1.112 (0.587–2.107) | p = 0.745 |
| Others               | 27 (15.0%)       | 27 (15.0%)            | 1.015 (0.565–1.824) | p = 0.959 |
| PASI #               |                  |                       |                   |          |
| <10                  | 97 (53.9%)       | 99 (55.3%)            | 1.00              |          |
| ≥10                  | 83 (46.1%)       | 80 (44.7%)            | 0.944 (0.623–1.431) | p = 0.787 |
| Onset (age, on skin) |                  |                       |                   |          |
| <40                  | 151 (83.9%)      | 153 (85.0%)           | 1.00              |          |
| ≥40                  | 29 (16.1%)       | 27 (15.0%)            | 0.919 (0.519–1.625) | p = 0.771 |
| Arthritis pain       |                  |                       |                   |          |
| No                   | 127 (70.6%)      | 114 (63.3%)           | 1.00              |          |
| Yes                  | 53 (29.4%)       | 66 (36.7%)            | 1.387 (0.892–2.157) | p = 0.145 |

4. Discussion

The present study, for the first time, investigated the role of ABCG2 polymorphism as a possible genetic risk factor for psoriasis. We found significant differences in genotype frequencies of ABCG2 rs2231142 between the psoriasis group and control population. Specifically, GT/TT genotypes of ABCG2 rs2231142 were associated with a reduced risk of psoriasis and were more prone to develop hyperuricemia in psoriasis patients. The correlation between GT/TT genotypes of the rs2231142 polymorphism and increased serum urate levels found in our cohort was consistent with previous reports in the Japanese and Han Chinese populations [29,30].

The link between psoriasis and ABCG2 gene polymorphisms implies that the polymorphic alleles may possess a protective effect from developing this cutaneous disease. Intriguingly, similar findings concerning the association of psoriasis with the IL12B and IL23R gene polymorphisms were documented in previous studies [31,32]. The polymorphic allele of ABCG2 rs2231142 is a missense variant that leads to a glutamine-to-lysine amino acid substitution (Q141K) in the exon 5 as a consequence of contributing to lower ABCG2 protein expression [22,33]. The role of ABCG2 in inflammatory diseases has been described in rheumatoid arthritis and psoriasis [19–21]. The phenomenon that functionality of ABCG2 was correlated with the disease activity in patients with recently diagnosed rheumatoid arthritis could be due to an inherent feature of lymphocytes [19]. The observation of marked ABCG2 expression in peripheral mononuclear cells from psoriasis seems to be consistent with our genetic findings since the predominant genotype (GG), known to be associated with higher transcription activities, was found to be more common in the psoriasis population than the control group. However, these results are contradictory to previous studies indicating a suppressive effect of ABCG2 on inflammatory signaling pathways [2]. To solve this contradiction, further in-depth investigation on the role of ABCG2 in psoriasis pathogenesis is warranted. Moreover, another ABCG2 SNP rs1448784 was located within the 3′-untranslated region and found to confer great susceptibility to gout [34]; this could be taken into consideration in future studies, in addition to the two most commonly studied missense SNPs, rs2231137 and rs2231142.

High levels of serum uric acid are frequently observed in patients with psoriasis. However, the actual causal relationship between psoriasis and hyperuricemia remains unknown. As psoriasis and hyperuricemia are affected by a number of shared and separated genetic
factors, a significantly higher level of uric acid was detected in psoriasis patients from the west but not from middle Asia and India in comparison with controls [35,36], indicating an ethnicity-specific correlation between psoriasis and hyperuricemia. In psoriasis, uric acid is considered as a byproduct of rapid skin cell turnover and systemic inflammation. Our observation that patients who carried at least one polymorphic allele (presumably leading to lower ABCG2 protein expression) of rs2231142 showed higher serum urate levels is in concert with the proposed function of ABCG2 as a high-capacity urate exporter. It is worth noting that, while no significant difference in serum urate levels was seen between our case and the control group, our genotyping results revealed a protective effect of the ABCG2 genetic polymorphism on psoriasis.

Our data revealed an influence of ABCG2 gene variations on the predisposition to psoriasis; however, there are several limitations in this study. First, the findings reported in this study may be unable to be extended to other ethnic groups unless replication cohorts are assessed. Second, the control group in this hospital-based study was recruited from individuals that may have psoriasis-like skin conditions which we could not exclude entirely. Another issue is that since the difference in age between the two study groups was significant and considerable, we corrected the associations for age but did not correct for other parameters. Additionally, more functional experiments are needed to determine the role of ABCG2 in the pathogenesis of psoriasis.

5. Conclusions

In conclusion, the present study revealed the novel finding that ABCG2 rs2231142 polymorphism was associated with psoriasis, indicating a link of altered ABCG2 expression or function to psoriasis pathogenesis.

Author Contributions: Conceptualization, Y.-H.H., S.-F.Y. and S.-C.S.; formal analysis, S.-F.Y., L.-C.C. and S.-C.S.; resources, Y.-H.H., L.-C.S., Y.-C.C. and W.-H.C.; writing—original draft preparation, Y.-H.H., S.-F.Y. and S.-C.S.; writing—review and editing, Y.-H.H., S.-F.Y. and S.-C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by research grants from Chang Gung Memorial Hospital to SCS (BMRPE97), YCC (CMRPG1F0063) and YHH (BMRPF30) and from Ministry of Science and Technology (MOST 108-2314-B-182A-106).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Chang Gung Medical Foundation, Taiwan (No. 201503178B0).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We thank Tissue Bank at Chang Gung Memorial Hospital, Keelung for sample preparation.

Conflicts of Interest: The authors declare no conflict of interest.

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