Ann Dermatol Vol. 26, No. 3, 2014 http://dx.doi.org/10.5021/ad.2014.26.3.343

ORIGINAL ARTICLE

Association of *CYP2C9* Genetic Variants with Vitiligo

Abdullateef A. Alzolibani, Ahmad Al Robaee, Hani Al-Shobaili, Fahad Al-Saif[1], Eman Al-Mekhadab[1], Ahmed A. Settin[2]

Department of Dermatology, College of Medicine, Qassim University, Buraidah,
[1]Department of Dermatology, College of Medicine, King Saud University, Riyadh,
[2]Research Centre, College of Medicine, Qassim University, Buraidah, Saudi Arabia

Background: Vitiligo is a depigmenting skin disorder in which genetic factors play an important role. **Objective:** To examine the association of *CYP2C9 *1/*2/*3* gene polymorphism with vitiligo. **Methods:** In this case controlled study, 95 Saudi patients with vitiligo (50 men and 45 women), with a mean age of 27.3 years, were analyzed. Patients were compared to 86 healthy controls from the same locality (76 men and 10 women), with a mean age of 20.1 years. In all participants, DNA was extracted and processed for characterization of *2C9 *1/*2/*3* gene variants using real time-polymerase chain reaction. **Results:** Vitiligo patients have a significantly higher *CYP2C9 *3* allele carriage rate compared to controls (32.7% versus 4.7%, $p=0.00$, odds ratio = 9.9, 95% confidence interval = 3.3 ~ 29.6). On the other hand, frequencies of *CYP2C9 *2* genotypes and alleles did not show any significant difference between vitiligo cases and controls. When the frequencies of *CYP2C9* genotypes were compared among subgroups of age, gender, family history, and disease patterns, the cases with positive consanguinity had significantly higher frequencies of homozygous genotypes than others ($p=0.029$). **Conclusion:** *CYP2C9 *3* allele carriage is probably associated with vitiligo susceptibility. **(Ann Dermatol 26(3) 343 ~ 348, 2014)**

-Keywords-
CYP2C9, Genetic polymorphism, Vitiligo

INTRODUCTION

Vitiligo is an acquired skin depigmentation that affects all races but is far more disfiguring in blacks. The precise cause of vitiligo is unknown[1]. An autoimmune process targeting melanocytes is considered to mediate its pathogenesis. Consistent with this hypothesis histological studies have reported the absence of melanocytes in the affected skin[2]. In addition to cellular immunity, multiple autoantibodies against melanocyte antigens including various enzymes and other substances have been detected in the sera of some patients with vitiligo[3,4]. Since genetic factors appear to play a role, 20% to 30% of patients were reported with a positive family history of the disorder[5,6]. Nevertheless, many vitiligo patients have neither a family history of vitiligo nor a history of other autoimmune diseases[6]. Consequently, many other hypotheses have been proposed to explain the pathogenesis of this disorder, including an inadequate defense from the toxic effects of free radicals and exposure of industrial chemicals[7,8]. These effects were hypothesized to be controlled by the variable expression of cytochrome P450 (*CYP* or P450) genes that encode a superfamily of multi-functional monooxygenases, which comprise more than 6,000 individual enzymes[9]. *CYP*s play a major role in the metabolism of foreign lipophilic compounds, including drugs and chemical carcinogens, as well as endogenous compounds such as steroids, fat-soluble vitamins, fatty acids, and biogenic amines[9]. In addition, *CYP* expression and activity can be in uenced by various factors such as genetic variations, presence of inhibitors or inducers, and disease states with differential tissue-specific expression pattern including the

Received November 9, 2012, Revised July 1, 2013, Accepted for publication July 9, 2013

Corresponding author: Abdullateef A. Alzolibani, Department of Dermatology, Qassim Medical College, P.O Box 30109 Buraidah 51477, Saudi Arabia. Tel: 966-16-3800050, Fax: 966-16-3801228, E-mail: azolibani@yahoo.com

skin[10-15].

The polymorphisms of important *CYP450* genes such as *CYP2C9*, *CYP2C19*, *CYP2D6*, and *CYP2E1* have been studied extensively in a large number of populations and showed a significant heterogeneity in the frequency of different alleles/genotypes and consequently in the resulting metabolizer phenotypes. Cytochrome P/450/*2C9* (*CYP2C9*) is primarily localized in the liver but can be expressed in other tissues like the skin. This enzyme belongs to the subfamily cytochrome *2C*, which comprise *CYP2C9* and 3 isoenzymes, *2C8*, *2C18*, and *2C19*[16]. The *CYP2C9* gene is polymorphic and within the inactive alleles *2C9*2*, **3*, **6*, **15*, and **25*, only **2* and **3* occur more frequently in Caucasians. In *2C9 *2* (rs 1799853) the amino acid arginine Arg 144 is replaced by Cys while in *2C9 *3* (rs 1057910) Ile 359 is replaced by Leu[17,18]. Variations in *CYP2C9* can be detected by real time polymerase chain reaction (PCR) using Taqman probes or probe-based melting curve analysis with the light cycler instrument[17,18]. This work aims to investigate the association of slow or mutant metabolizer variants of *CYP2C9* gene; **2* and **3* with vitiligo among Saudi patients.

MATERIALS AND METHODS

This is a case controlled study on 95 Saudi vitiligo cases in addition to a control sample of 86 healthy unrelated subjects from the same locality. Cases included 50 men and 45 women with a mean age of 27.3 ± 14.5 years and a median age of 23 years. They were recruited from the Outpatient Dermatology Clinics affiliated to Qassim University and King Saud University, Saudi Arabia from January to August 2012. Diagnosis of vitiligo was made by a consultant dermatologist. The detected vitiligo cases were of focal (22 cases), vulgaris (52 cases), acrofacial (20 cases), and universal (1 case) types. The clinical classification of Hercogová et al.[19], was used for the categorization of focal vitiligo as localized lesions that are clinically and pathologically typical of vitiligo presenting in the form of one or more macules in one area, but not clearly in a segmental distribution.

Among these cases, 39 (41.1%) patients had positive family history of vitiligo, whereas 32 (33.7%) patients had positive parental consanguinity. Patients' data were compared with that of the control subjects, which comprised 76 men and 10 women with a mean age of 20.1 ± 3.3 years. An informed consent was obtained from all participants and the study was approved by the Scientific and Ethical Committees of Qassim University, Saudi Arabia.

Blood samples were taken from all participants and DNA was isolated from the peripheral blood using a MagNA Pure LC instrument (LC DNA Isolation Kit LV; Roche Molecular Biochemicals, Mannheim, Germany).

Oligonucleotide primers and fluorescence-labeled hybridization probes were designed for amplification and sequence-specific detection of both *CYP2C9 *2* and *2C9 *3* (TIB MolBiol, Berlin, Germany). The master mix used in the PCR reaction contained $2\ \mu$l of a $10\times$mixture of LightCycler FastStart DNA master hybridization probes, 5 mM $MgCl_2$ (final concentration), $1\ \mu$M final concentration of primers, $0.075\ \mu$M final concentration of specific primers, and $0.2\ \mu$M final concentration of hybridization probes. Real time PCR was done using LightCycler instrument (Roche Diagnostics, Mannheim, Germany). The specificity of the amplified product was confirmed by corresponding melting curve analysis.

Statistical analysis

Statistical analysis was performed using the statistical software program SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Comparisons between cases and controls' genotype and allele frequencies were done using the chi-square test and odds ratio (with 95% confidence intervals). In addition, conformity to the Hardy Weinberg law of genetic equilibrium was tested among cases and controls using the chi square test through the assessment of the difference between the frequencies of the observed and the expected genotypes. A p-value <0.05 was considered statistically significant.

RESULTS

Normal controls showed 5 different genotypic variants including *CYP2 C9 *1/*1*, **1/*2*, **1/*3*, **2/*2*, **2/*3*, and **3/*3* with frequencies of 67.4%, 22.1%, 3.5%, 5.8%, 1.2%, and 0.0% respectively. Vitiligo patients had significantly higher *CYP2C9 *3* allele carriage rate (both **1/*3*, **2/*3*, and **3/*3* genotypes) compared to controls (32.7% vs. 4.7%, $p=0.00$, odds ratio [OR]=9.9, 95% confidence interval [CI]=3.3~29.6). This was confirmed by the higher *CYP2C9 *3* allele frequency among patients compared to controls (16.8% vs. 2.3%, OR=8.1, 95% CI=2.8~23.4, $p=0.0$; Table 1). Interestingly, statistical analysis of the vitiligo cases excluding the focal type that is liable for mistyping, according to a recent classification, has confirmed the previous results indicating a significantly higher *CYP2C9 *3* allele frequency among cases compared to controls (17.12% vs. 2.3%, OR=8.4, 95% CI=2.8~24.8, $p=0.0$; data not shown). On the other hand, frequencies of *CYP2C9 *2* genotypes and alleles did not show any significant difference between vitiligo cases and controls ($p>0.05$; Table 1). Conformity to the Hardy

Table 1. Frequency of *CYP2C9 *1/*2/*3* polymorphism in vitiligo cases compared to controls

CYP2C9 locus **2*	*CYP2C9* locus **3*	Final genotype	Case (n=95)	Control (n=86)
**1/*1*	**1/*1*	**1/*1*	46 (48.4)	58 (67.4)
**1/*2*	**1/*1*	**1/*2*	16 (16.8)	19 (22.1)
**1/*1*	**1/*3*	**1/*3*	29 (30.5)	3 (3.5)
**2/*2*	**1/*1*	**2/*2*	2 (2.1)	5 (5.8)
**1/*2*	**1/*3*	**2/*3*	1 (1.1)	1 (1.2)
**1/*1*	**3/*3*	**3/*3*	1 (1.1)	0 (0.0)
	HWE (*CYP2C9* locus **2*)		$\chi^2=82.7$, $p\leq0.001$ †	$\chi^2=62$, $p\leq0.001$ †
	HWE (*CYP2C9* locus **3*)		$\chi^2=1.5$, $p\geq0.05$	$\chi^2=0.05$, $p\geq0.05$
	CYP2C9 allele		Case (n=190)	Control (n=172)
	*Allele *1*		137 (72.11)	138 (80.23)
	*Allele *2*		21 (11.05)	30 (17.44)
	*Allele *3*		32 (16.84)	4 (2.33)
	*Allele *2 vs. *1*		$p=0.3$, OR (95% CI)=0.7 (0.4~1.3)	
	*Allele *3 vs. *1*		$p=0.0$ †, OR (95% CI)=8.1 (2.8~23.4)	

Values are presented as number (%) or median (range). HWE: Hardy Weinberg Equilibrium, OR: odds ratio, CI: confidence interval. †Marks indicate significant difference, $p<0.05$.

Table 2. Frequency of *CYP2C9 *2* and **3* alleles and genotypes in Saudi cases of vitiligo related to their demographic data and the pattern of the disease

	Homozygous normal (**1/*1*)	Heterozygous mutant (**1/*2* & **1/*3*)	Homozygous mutant (**2/*3* & **2/*2* & **3/*3*)	*p*-value
Age (yr)				
≤20 (n=33)	15 (46.9)	16 (46.9)	2 (6.3)	0.77
>20 (n=62)	31 (51.7)	29 (45.0)	2 (3.3)	
Gender				
Male (n=50)	27 (56.3)	21 (39.6)	2 (4.2)	0.45
Female (n=45)	19 (43.2)	24 (52.3)	2 (4.5)	
Family history				
Positive (n=39)	20 (52.6)	16 (39.5)	3 (7.9)	0.30
Negative (n=56)	25 (48.1)	29 (50.0)	1 (1.9)	
Consanguinity				
Positive (n=31)	21 (67.7)	8 (25.8)	2 (6.5)	0.029†
Negative (n=64)	25 (41.7)	37 (55.0)	2 (3.3)	
Pattern				
Focal (n=22)	12 (63.2)	10 (36.8)	0 (0.0)	0.58
Vulgaris (n=52)	25 (48.1)	25 (48.1)	2 (3.8)	
Acrofacial (n=20)	9 (45.0)	9 (45.0)	2 (10.0)	
Universal (n=1)	0 (0.0)	1 (100.0)	0 (0.0)	

Values are presented as number (%). †Mark indicates significant difference, $p<0.05$.

Weinberg Equilibrium (HWE) was noted in *CYP2C9*3* locus variants among cases and controls, which did not show any significant difference between the expected and observed genotypes ($p>0.05$). However, *CYP2C9*2* variants showed significant difference between expected and observed frequencies of polymorphic genotypes ($p<0.001$; Table 1).

Combined *CYP2C9 *2* and **3* genotypic variants confirmed the higher frequency of the heterozygous mutant forms **2/*1* and **3/*1* genotypes among cases compared to controls (47.4% vs. 25.6%) and a lower frequency of **1/*1* (48.4% vs. 67.4%). Comparison of the frequencies of *CYP2C9* normal, heterozygous, and homozygous mutant genotypes among subgroups of age, gender, family history, and disease patterns indicated insignificant difference. On the other hand, cases with positive consanguinity showed higher homozygous genotypes than others ($p=0.029$; Table 2).

DISCUSSION

Cytochrome P450 *2C9* has been suggested to be very similar to epoxide hydrolase (sEH), which hydrolyzes a wide variety of endogenous and exogenous epoxides that are believed to be formed by cytochrome P450 epoxygenases. Moreover, sEH was found in various tissues including the epithelial cells in the skin[20]. In active vitiligo patients, an increase in oxidative stress in the entire epidermal compartment has been demonstrated; in particular, the imbalance in catalase activity, reduced glutathione, and vitamin E levels was associated with hyperproduction of reactive oxygen species[21-23]. Oxidative DNA damage in vitiligo patients manifested by DNA breakage in mononuclear leukocytes was shown to be comparatively higher[24]. Since these factors might contribute to the susceptibility to vitiligo, we have undertaken this research to clarify the association of *CYP2C9* gene polymorphism with vitiligo among Saudi patients.

Frequencies of *CYP2C* variants among normal Saudi subjects showed a relatively unique pattern in the form of high carrier rate of **2* allele (**1/*2*, **2/*3*, and **2/*2* genotypes), which was 29.1% of controls that was much higher than the carriage rate for the allele **3* (**1/*3*, **2/*3*, and **3/*3*) which was 4.7%, thus resulting into allele frequencies of 17.44% and 2.33% for alleles **2* and **3*, respectively. In this respect, we would note that normal Saudi subjects had a lower carriage rate and allele frequency of *CYP 2C *3* when compared to Iranians and Caucasians, whose carriage rate was as high as 5% to 10%[16,25,26], but relatively closer to that of the Asian Indians, Korean, Chinese, Hispanics, and African Americans whose carriage rate was 2% to 4%[26-30].

Interestingly, the Saudi vitiligo patients showed a significantly higher frequencies of **3* allele carriage rate corresponding to 32.7% of cases with a significantly higher **3* allele frequency of 16.84% but with a lower **2* allele frequency (11.05%) that was statistically insignificant compared to controls. This suggests the potential association of *CYP2C9 *3* with the susceptibility to vitiligo, in this particular population. However, it is not clear whether this susceptibility is due to a primary genetic predisposition or secondary to an error related to the metabolism of certain chemicals or other environmental agents. Since *CYP2C9* is an oxidative metabolizer of exogenous drugs and toxins as well as endogenous polypeptide enzymes and hormones, we can speculate that the slow metabolizing genetic form of the **3* allele predisposes the patient skin to oxidative stress probably under the effect of inhibitory drugs or toxins to the natural enzymes involved in melanin synthesis. Furthermore, the oxidative stress hypothesis is supported by the higher hydrogen peroxide levels in vitiligo epidermis that was previously attributed to factors like catalase genetic polymorphisms, reduced glutathione peroxidase activity and increased levels of tetrahydrobiopterins (6BH4 and 7BH4), which are inhibitors of tyrosinase,and phenyl alanine hydroxylase enzymes[31,32].

We propose an extensive analysis of all potential forms of exposure to chemicals, drugs, pollutants or radiations for all affected subjects probably using investigative techniques like HPLC. Genome wide association studies indicated that most vitiligo susceptibility loci (more than 20) encode immunoregulatory proteins or melanocyte components that likely mediate immune targeting and genetic relationships among vitiligo, malignant melanoma, and normal variation of eye, skin, and hair color[33,34]. These loci are distributed along diverse chromosomal locations including the chromosome 10q22-23 in areas nearby the area coding the *CYP2C9* (10q24). A strong association with a single nucleotide polymorphism within the major histocompatibility complex region had been also identified in a recent genome-wide association study of generalized vitiligo[35].

Since degradation of drugs in humans is driven by detoxification mechanisms whose efficiency is influenced by genetic mutations, Weise et al.[36] studied the association between type 2 diabetes with mutations in prominent members of the *CYP* 450 2C9 isoenzyme family.

Probable genetic contribution to the occurrence of vitiligo among Saudi subjects is relatively higher in patients with positive family history (41.1%) and consanguinity (33.7%). This study, demonstrated that consanguinity apparently had a role into the appearance of homozygous genotypes although most of them were for the normal or wild type allele *1 with some mutant forms. On the other hand, the distribution of genetic variants of *CYP2C9* were not affected by age, gender, family history or pattern of vitiligo among the patients. The gene frequencies related to the *CYP 2C*3* allele were in conformity with the HWE. In contrast, gene frequencies related to allele **2* were not in accordance to the HWE that might be due to higher levels of consanguinity or due to the relatively small sized sample. So, this research probably needs to be investigated in a wider study by including other interactive haplotypes and genetic polymorphisms as suggested by other scientists[37].

Interestingly, Saudi cases did not show any significant difference from the control subjects in terms of the frequency of their *CYP2C9 *2* allelic variants. Similarly, Semiz et al.[38] reported that no significant difference in allele frequencies for *CYP2C9 *2*, was demonstrated between diabetic and non-diabetic subjects. Recently, Kaur-Knudsen

et al.[39] reported the findings of large studies on the association between genetic variation in *CYP*1B1 and *CYP2C9* and the risk of disease, and rebutted the hypotheses that these genetic variants?influenced the risk of tobacco-related cancer, female cancer (as cervical and endometrial cancers), chronic obstructive pulmonary disease, and ischemic vascular disease. Veenstra et al.[18] found that genetic variation in *CYP2C9* exons, rather than the promoter or other regulatory regions, is largely responsible for warfarin sensitivity associated with *CYP2C9* variants in a European American population. Other studies have reported that *CYP2C9 *3* genotype did not affect the required warfarin dose while it was associated with increased risk of bleeding when treated with routine dosage regimen during the initiation of treatment[40].

In conclusion, this study provides presumptive evidence that *CYP2C9 *3* is probably associated with the susceptibility to vitiligo among Saudi subjects regardless of the clinical pattern, gender, and presence of family history. Nonetheless, our study is limited in terms of the relatively small sample size, lack of protein studies or cell culture analyses to fully examine the underlying mechanism of vitiligo pathogenesis.

ACKNOWLEDGMENT

Authors are grateful to the Deanship of Research and Postgraduate Studies, Qassim University, Saudi Arabia for completely sponsoring this study.

REFERENCES

1. Grimes PE. New insights and new therapies in vitiligo. JAMA 2005;293:730-735.
2. van den Wijngaard R, Wankowicz-Kalinska A, Le Poole C, Tigges B, Westerhof W, Das P. Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes is associated with the prominent presence of CLA+ T cells at the perilesional site. Lab Invest 2000;80:1299-1309.
3. Ongenae K, Van Geel N, Naeyaert JM. Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res 2003;16:90-100.
4. Kemp EH, Waterman EA, Hawes BE, O'Neill K, Gottumukkala RV, Gawkrodger DJ, et al. The melanin-concentrating hormone receptor 1, a novel target of autoantibody responses in vitiligo. J Clin Invest 2002;109:923-930.
5. Majumder PP, Nordlund JJ, Nath SK. Pattern of familial aggregation of vitiligo. Arch Dermatol 1993;129:994-998.
6. Handa S, Kaur I. Vitiligo: clinical findings in 1436 patients. J Dermatol 1999;26:653-657.
7. O'Sullivan JJ, Stevenson CJ. Screening for occupational vitiligo in workers exposed to hydroquinone monomethyl ether and to paratertiary-amyl-phenol. Br J Ind Med 1981; 38:381-383.
8. Schallreuter KU, Wood JM. Free radical reduction in the human epidermis. Free Radic Biol Med 1989;6:519-532.
9. Bièche I, Narjoz C, Asselah T, Vacher S, Marcellin P, Lidereau R, et al. Reverse transcriptase-PCR quantification of mRNA levels from cytochrome (CYP)1, CYP2 and CYP3 families in 22 different human tissues. Pharmacogenet Genomics 2007;17:731-742.
10. Orellana M, Guajardo V. Cytochrome P450 activity and its alteration in different diseases. Rev Med Chil 2004;132:85-94.
11. Spiecker M, Darius H, Hankeln T, Soufi M, Sattler AM, Schaefer JR, et al. Risk of coronary artery disease associated with polymorphism of the cytochrome P450 epoxygenase CYP2J2. Circulation 2004;110:2132-2136.
12. Hoffmann MM, Bugert P, Seelhorst U, Wellnitz B, Winkelmann BR, Boehm BO, et al. The -50G>T polymorphism in the promoter of the CYP2J2 gene in coronary heart disease: the Ludwigshafen Risk and Cardiovascular Health study. Clin Chem 2007;53:539-540.
13. Delozier TC, Kissling GE, Coulter SJ, Dai D, Foley JF, Bradbury JA, et al. Detection of human CYP2C8, CYP2C9, and CYP2J2 in cardiovascular tissues. Drug Metab Dispos 2007;35:682-688.
14. Boxenbaum H. Cytochrome P450 3A4 in vivo ketoconazole competitive inhibition: determination of Ki and dangers associated with high clearance drugs in general. J Pharm Pharm Sci 1999;2:47-52.
15. Gras J, Llenas J. Effects of H1 antihistamines on animal models of QTc prolongation. Drug Saf 1999;21 Suppl 1:39-44; discussion 81-87.
16. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 2005;7:97-104.
17. Burian M, Grösch S, Tegeder I, Geisslinger G. Validation of a new fluorogenic real-time PCR assay for detection of CYP2C9 allelic variants and CYP2C9 allelic distribution in a German population. Br J Clin Pharmacol 2002;54:518-521.
18. Veenstra DL, Blough DK, Higashi MK, Farin FM, Srinouanprachan S, Rieder MJ, et al. CYP2C9 haplotype structure in European American warfarin patients and association with clinical outcomes. Clin Pharmacol Ther 2005;77:353-364.
19. Hercogová J, Schwartz RA, Lotti TM. Classification of vitiligo: a challenging endeavor. Dermatol Ther 2012;25 Suppl 1:S10-S16.
20. Enayetallah AE, French RA, Thibodeau MS, Grant DF. Distribution of soluble epoxide hydrolase and of cytochrome P450 2C8, 2C9, and 2J2 in human tissues. J Histochem Cytochem 2004;52:447-454.
21. Schallreuter KU, Wood JM, Berger J. Low catalase levels in the epidermis of patients with vitiligo. J Invest Dermatol 1991;97:1081-1085.
22. Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S, et al. Increased sensitivity to peroxidative agents as a

possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol 1997;109:310-313.
23. Dell'Anna ML, Maresca V, Briganti S, Camera E, Falchi M, Picardo M. Mitochondrial impairment in peripheral blood mononuclear cells during the active phase of vitiligo. J Invest Dermatol 2001;117:908-913.
24. Giovannelli L, Bellandi S, Pitozzi V, Fabbri P, Dolara P, Moretti S. Increased oxidative DNA damage in mononuclear leukocytes in vitiligo. Mutat Res 2004;556:101-106.
25. Hashemi-Soteh SM, Shahabi-Majd N, Gholizadeh AR, Shiran MR. Allele and genotype frequencies of CYP2C9 within an Iranian population (Mazandaran). Genet Test Mol Biomark 2012;16:817-821.
26. Xie HG, Prasad HC, Kim RB, Stein CM. CYP2C9 allelic variants: ethnic distribution and functional significance. Adv Drug Deliv Rev 2002;54:1257-1270.
27. Rathore SS, Agarwal SK, Pande S, Mittal T, Mittal B. Frequencies of VKORC1 -1639 G>A, CYP2C9*2 and CYP2C9*3 genetic variants in the Northern Indian population. Biosci Trends 2010;4:333-337.
28. Lee HW, Lim MS, Lee J, Jegal MY, Kim DW, Lee WK, et al. Frequency of CYP2C9 variant alleles, including CYP2C9*13 in a Korean population and effect on glimepiride pharmacokinetics. J Clin Pharm Ther 2012;37:105-111.
29. Yang ZF, Cui HW, Hasi T, Jia SQ, Gong ML, Su XL. Genetic polymorphisms of cytochrome P450 enzymes 2C9 and 2C19 in a healthy Mongolian population in China. Genet Mol Res 2010;9:1844-1851.
30. Scibona P, Redal MA, Garfi LG, Arbelbide J, Argibay PF, Belloso WH. Prevalence of CYP2C9 and VKORC1 alleles in the Argentine population and implications for prescribing dosages of anticoagulants. Genet Mol Res 2012;11:70-76.
31. Schallreuter KU, Moore J, Wood JM, Beazley WD, Gaze DC, Tobin DJ, et al. In vivo and in vitro evidence for hydrogen peroxide (H2O2) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase. J Investig Dermatol Symp Proc 1999;4:91-96.
32. Schallreuter KU, Moore J, Wood JM, Beazley WD, Peters EM, Marles LK, et al. Epidermal H(2)O(2) accumulation alters tetrahydrobiopterin (6BH4) recycling in vitiligo: identification of a general mechanism in regulation of all 6BH4-dependent processes? J Invest Dermatol 2001;116:167-174.
33. Jin Y, Birlea SA, Fain PR, Ferrara TM, Ben S, Riccardi SL, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. Nat Genet 2012;44:676-680.
34. Tang XF, Zhang Z, Hu DY, Xu AE, Zhou HS, Sun LD, et al. Association analyses identify three susceptibility Loci for vitiligo in the Chinese Han population. J Invest Dermatol 2013;133:403-410.
35. Tang J, Liu JL, Zhang C, Hu da Y, He SM, Zuo XB, et al. The association between a single nucleotide polymorphism rs11966200 in MHC region and clinical features of generalized vitiligo in Chinese Han population. Mol Biol Rep 2013;40:4097-4100.
36. Weise A, Prause S, Eidens M, Weber MM, Kann PH, Forst T, et al. Prevalence of CYP450 gene variations in patients with type 2 diabetes. Clin Lab 2010;56:311-318.
37. Pedersen RS, Brasch-Andersen C, Sim SC, Bergmann TK, Halling J, Petersen MS, et al. Linkage disequilibrium between the CYP2C19*17 allele and wildtype CYP2C8 and CYP2C9 alleles: identification of CYP2C haplotypes in healthy Nordic populations. Eur J Clin Pharmacol 2010;66:1199-1205.
38. Semiz S, Dujic T, Ostanek B, Prnjavorac B, Bego T, Malenica M, et al. Analysis of CYP2C9*2, CYP2C19*2, and CYP2D6*4 polymorphisms in patients with type 2 diabetes mellitus. Bosn J Basic Med Sci 2010;10:287-291.
39. Kaur-Knudsen D, Bojesen SE, Nordestgaard BG. Cytochrome P450 1B1 and 2C9 genotypes and risk of ischemic vascular disease, cancer, and chronic obstructive pulmonary disease. Curr Vasc Pharmacol 2012;10:512-520.
40. Liu Y, Zhong SL, Tan HH, Yang M, Fei HW, Yu XY, et al. Impact of CYP2C9 and VKORC1 polymorphism on warfarin response during initiation of therapy. Zhonghua Xin Xue Guan Bing Za Zhi 2011;39:929-935.