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# *PRKCQ* rs4750316 is associated with Vogt-Koyanagi-Harada syndrome in a Han Chinese population

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**Purpose:** The *PRKCQ* and *REL* genes are said to be associated with multiple autoimmune diseases. This study investigated the association between these genes and Vogt-Koyanagi-Harada (VKH) syndrome in Han Chinese.
**Methods:** A two-stage case−control study was performed on three single nucleotide polymorphisms ([SNPs] rs4750316, rs11258747, and rs947474) of the *PRKCQ* gene and three SNPs (rs842647, rs702873, and rs13031237) of the *REL* gene using PCR–restriction fragment length polymorphism (PCR-RFLPs) in a total of 859 patients with VKH syndrome and 1,542 healthy controls. Variables such as extraocular presentations were assessed. The data were analyzed using chi-square analysis, and corrected for multiple comparisons with the Bonferroni method.
**Results:** We found a decreased frequency of the GC genotype and the C allele of rs4750316 in patients with VKH syndrome when the GG genotype or G allele was used as a reference, respectively (GC genotype: $P$ =2.45e-10, odds ratio [OR]=0.37, 95% confidence interval [CI]=0.28–0.51; C allele: $P$=8.79e-10, OR=0.41, 95% CI=0.31–0.55). The genotypic and allelic frequencies of rs11258747, rs947474, rs842647, rs702873, and rs13031237 were not statistically significantly different between patients with VKH syndrome and controls. Stratification analysis indicated that the *PRKCQ* rs4750316 polymorphism was associated with patients with VKH syndrome experiencing headache, alopecia, poliosis, tinnitus, and dysacusia, but no statistically significant association of the other five SNPs was found.
**Conclusions:** The *PRKCQ* rs4750316 polymorphism may be a susceptibility factor for VKH syndrome pathogenesis and extraocular presentations, indicating that *PRKCQ* may be involved in the pathogenesis and extraocular presentations of VKH syndrome through the T-cell receptor (TCR) signaling pathway.

Vogt−Koyanagi−Harada (VKH) syndrome is a multisystemic inflammatory disease characterized by bilateral diffuse granulomatous panuveitis with neurologic symptoms (such as tinnitus, dysacusis, vertigo, meningismus, cerebrospinal fluid pleocytosis) and cutaneous changes (such as alopecia, poliosis, vitiligo [1], and auditory symptoms [2,3]). VKH syndrome has a variable incidence, and is more prevalent in Asia [4], India, Iran [5], as well as among Hispanic and Native American individuals [6] and those of Mediterranean origin [7]. This syndrome is rare in Caucasians and individuals of Turkish descent [8-12]. In addition, VKH syndrome primarily affects middle-aged women [2,13]. Although the etiology of VKH syndrome remains elusive, it is generally considered that the interaction of genetic variants with environmental risk factors contributes to its development. Genome-wide association studies (GWASs) have identified the predominant VKH syndrome susceptibility loci, which include *human leukocyte antigen (HLA)-DR4* (ID:3126), *DR53* (ID: 282811), *HLA*-DRB1 (ID: 3123, OMIM: 142857), *HLA-DQA1* (ID: 3117, OMIM: 146880), *HLA*-DQB1 (ID: 3119, OMIM: 604305), and *non-HLA* genes, such as *IL23R* (ID:149233, OMIM: 607562) -*C1orf141* (ID:400757) and *ADO* (ID:84890, OMIM: 611392)-*ZNF365* (ID:22891, OMIM: 607818)-*EGR2* (ID:1959, OMIM: 129010) [14,15]. Candidate gene association studies have searched for additional VKH syndrome genes, including the *CLEC16A* (ID:23274, OMIM: 611303) and *JAK1* (ID:3716, OMIM: 147795) [16] genes, and the *CD40* gene (ID:958, OMIM: 109535) in Chinese patients [17]. However, the genes that have been associated with VKH syndrome do not fully account for its pathogenesis, and more novel VKH syndrome susceptibility loci still need to be identified.

The *PRKCQ* (ID:5588; OMIM: 600448) gene, encoding the protein kinase-C-theta (PKC-θ), plays a critical role in T-lymphocyte activation, differentiation, and responses through T-cell receptor (TCR) signaling [18,19]. Previous studies have shown that PKC-θ controls T-cell activation in many models of inflammatory disorders, such as experimental autoimmune encephalomyelitis (EAE) [19], the allergic response to house dust mites [20], arthritis [21],

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and chronic colitis [22]. Moreover, the PKC-θ-deficient T cells in mice show impaired differentiation toward T-helper subsets, and a complex loss of cytokines [23]. In addition, PKC-θ is required for the activation of several transcription factors, such as nuclear factor-κ B (NF-κB), in inflammatory responses [23]. The *REL* gene (ID:5966, OMIM: 164910)—encoding c-Rel, which is a member of the NF-κB family with various functions in hematopoietic cells, antigen-presenting cells, and T cells—has been identified as a predisposition locus to several autoimmune diseases, such as rheumatoid arthritis (RA) [24,25], celiac disease (CD) [26], and Behcet's disease (BD) [27]. In previous studies, *Rel* knockout mice have been shown to not develop EAE and type I diabetes (TID) [28,29]. Because of the shared pathogenesis with other autoimmune diseases, it is plausible that gene polymorphisms of *PRKCQ* and *REL* involved in these diseases could be also predisposed to VKH syndrome. The three single nucleotide polymorphisms (SNPs) in the *PRKCQ* gene that were detected in the present study—that is, rs4750316, rs11258747, and rs947474—were selected as SNP candidates based on their associations with RA, psoriatic arthritis, and type 1 diabetes mellitus (T1DM) [30-32]. Because VKH syndrome is considered a T-cell-mediated immune disease, and thus, may share similar genetic risk factors, rs4750316, rs11258747, and rs947474 of *PRKCQ* were selected as candidate SNPs in the present study. The SNPs rs842647, rs702873, and rs13031237 in the *REL* gene were chosen as SNP candidates due to their encoding protein NF-κB c-Rel, which is required for the production of cytokines by human uveal melanocytes which are considered antigen-presenting cells in human VKH disease [33]. In this study, three *PRKCQ* SNPs (rs4750316, rs11258747, and rs947474) and three *REL* SNPs (rs842647, rs702873, and rs13031237) were chosen as candidate risk variants of VKH syndrome. This study detected lower frequencies of the rs4750136 GC genotype and rs4750316 C allele in patients with VKH syndrome according to the reference GG genotype or G allele. Stratified analysis also showed an association between the rs4750136 C allele polymorphism and headache, alopecia, poliosis, tinnitus, and dysacusia in patients with VKH syndrome.

## METHODS

*Ethics statement:* All the participants, including patients with VKH syndrome and controls, signed written informed consent before enrolling in this study. For pediatric patients with VKH syndrome, their parents signed written informed consent. All procedures followed the tenets of the Declaration of Helsinki and adhered to the ARVO statement on human subjects. Approval for the study was obtained from the Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and the Ethics Committee of Chongqing Medical University (Permit Number: 2009–201008).

*Study population:* Eight hundred fifty nine VKH patients (475 men and 384 women [mean age 39.7 years]) and 1542 healthy controls (861 men and 681 women [mean age 39.5 years]) were recruited from the First Affiliated Hospital of Chongqing Medical University (Chongqing, China) and Zhongshan Ophthalmic Center, Sun Yat-sen University (Guangzhou, China) between April 2005 and December 2013 in this two-stage study. All patients had clinical findings of intraocular inflammation. The healthy controls with no history of ocular or autoimmune disorders were matched in terms of age and geographic area of origin. All patients and controls were of Han Chinese descent. VKH syndrome was diagnosed according to the revised criteria for VKH disease [34]. In this two-stage study, 600 patients with VKH syndrome and 1,000 healthy controls were randomly selected from the whole patient and control populations to determine the susceptible SNPs ($p < 0.05$) in the first stage of the study. In the second stage, another 259 patients with VKH syndrome and 542 controls were added to replicate the associated SNPs identified in the first stage. The clinical characteristics of patients with VKH syndrome are summarized in Table 1.

*Genomic DNA extraction:* Peripheral blood collection were conducted by venipuncture from all the participants and stored at -80 °C until used. Extraction of genomic DNA was performed from the peripheral blood of controls and patients using the QIAmp DNA Blood Mini Kit (QIAGEN Inc., Hilden, Germany) according to the manufacturer's instructions; the samples were then frozen at −80 °C for future use.

*Gene genotyping and quality control:* PCR–restriction fragment length polymorphism (PCR-RFLP) was used to genotype *PRKCQ* polymorphisms (rs4750316, rs11258747, and rs947474) and *REL* polymorphisms (rs842647, rs702873, and rs13031237). The targeted DNA fragment of the *PRKCQ* and *REL* genes was amplified with PCR using the designed primers with Primer Premier 5.0, and the restriction enzymes are presented in Table 2. Each PCR reaction was performed in a 10-µl reaction system containing 5 µl of a Go Taq Green Master Mix (Promega Corporation, Madison, WI), 20 pmol of each primer, and 0.2 µg of genomic DNA. The following thermal-cycler conditions were conducted: 5 min at 95 °C, followed by 35 cycles of 30 s 95 °C, 40 s at different temperatures (62 °C for rs4750316, rs842647, rs702873, and rs13031237; 60 °C for rs11258747 and rs947474); 30 s at 72 °C; and 3 min at 72 °C. Digestion of PCR products of those SNPs was conducted with 2 U of *HpyCH4 III* (Thermo

Table 1. Clinical characteristics of the investigated VKH patients used for the first- and second-stage studies.

| Clinical characteristics | VKH patients in the first stage (total=600) | % | VKH patients in Second stage (total=259) | % |
|---|---|---|---|---|
| Age at onset (years ± SD) | 38.74±13.44 | | 41.96±14.21 | |
| Males | 327 | 54.50 | 148 | 57.1 |
| Females | 273 | 45.50 | 111 | 42.9 |
| Headache | 244 | 40.67 | 120 | 46.33 |
| Alopecia | 240 | 40.00 | 94 | 36.29 |
| Poliosis | 232 | 38.67 | 100 | 38.61 |
| Vitiligo | 106 | 17.67 | 48 | 18.53 |
| Tinnitus | 274 | 45.67 | 126 | 48.65 |
| Neck stiffness | 70 | 11.67 | 34 | 13.13 |
| Dysacusia | 188 | 31.33 | 101 | 38.40 |
| Scalp hypersensitivity | 94 | 15.67 | 40 | 15.44 |

Fisher Scientific Inc., Ontario, Canada), *Mwol* (New England BioLabs, Inc., Ontario, Canada), *DdeI* (Thermo Fisher Scientific), *HpyCH4 III* (Thermo Fisher Scientific), *BsiWI* (New England BioLabs, Inc.), and *Csp6I* (Thermo Fisher Scientific Inc.) restriction enzymes (Table 2) in a 10-µl reaction system for 12 to 16 h. Electrophoresis on a 4.5% agarose gel and stain with GoldView (SBS Genentech, Beijing, China) was used to separate the digestion products. Genotype results were assessed in a blinded manner, and repeats of all ambiguous samples were conducted. Moreover, to validate the results of the PCR-RFLP, 10% of the samples were double-checked using direct sequencing (Sangon Biotech, Co., Ltd., Shanghai, China).

*Statistical analysis:* Statistical analysis was performed using SPSS software version 17.0 for Windows (SPSS Inc., Chicago, IL). The Hardy–Weinberg equilibrium (HWE) was quantified by using the chi-square test. Genotype and allele frequencies were calculated with direct counting, and were compared between patients and controls using chi-squares. Logistic regression analysis was performed to assess the association of the tested SNPs with the extraocular manifestations. All statistical analyses were two-sided, and a p value of less than 0.05 was considered statistically significant.

## RESULTS

The distribution of the genotype frequencies of the six tested SNPs was in line with HWE in the case and control groups (p>0.05). Table 3 presents the genotype and allele frequencies of the three tested *PRKCQ* polymorphisms and *REL* polymorphisms in the cohort. In the first-stage study, 600 patients with VKH syndrome and 1,000 healthy controls were

Table 2. Primers and restriction enzymes used for RFLP analysis of the *PRKCQ* and *REL* genes.

| Gene | rs number | Primers | Restriction enzyme |
|---|---|---|---|
| *PRKCQ* | rs4750316 | 5′-GGAAGAGCTGATAAGGGAAATGTC-3′<br>5′-TCCAGAAGGGCCAGAACACTA-3′ | *HpyCH4III* |
| | rs11258747 | 5′-GGGTCAATCTCCTTCCGTTCA-3′<br>5′-TGCTCTGCTCCCTTTCAGCTCTT −3′ | *MwoI* |
| | rs947474 | 5′-ACCAGTTATGAAGGGTGACAAAGA-3′<br>5′- GATCAAATACCAACTGCGTTGACT-3′ | *DdeI* |
| *REL* | rs842647 | 5′-TGCTTGTCTCTGATTCTCTGGGTC-3′<br>5′-CTGGGCGACAAGTGTGAAACTC-3′ | *HpyCH4III* |
| | rs702873 | 5′-CAAAGCATCCTTCTTACTGGGTGT-3′<br>5′-AAGGCATTAGGAAGATTAGTGGTGTC-3′ | *BsiWI* |
| | rs13031237 | 5′-GAGTTGTTATGAGAGTAAAAGGCTGC-3′<br>5′-AAGTACACAAGTTCTGCCTAGGGTAA-3′ | *Csp6I* |

RFLP-restriction fragment length polymorphism.

Table 3. Frequencies of alleles and genotypes of *PRKCQ* and *REL* polymorphisms in VKH patients and controls in the first-stage study.

| SNP | Genotype allele | Cases (n=600) | Controls (n=1000) | *P* value | $P_c$ | OR (95% CI) |
|---|---|---|---|---|---|---|
| rs4750316 | GG | 554 (92.33) | 842 (84.2) | | | Reference |
| | GC | 44 (7.33) | 153 (15.3) | 2.50e-6 | 6.00e-5 | 0.44 (0.31–0.62) |
| | CC | 2 (0.34) | 5 (0.5) | 0.55 | NS | 0.61 (0.12–3.14) |
| | G | 1152 (96.00) | 1837(91.85) | | | Reference |
| | C | 48 (4.00) | 163 (8.15) | 4.66e-6 | 1.12e-4 | 0.47 (0.34–0.65) |
| rs11258747 | GG | 549 (91.50) | 867 (86.7) | | | Reference |
| | GT | 49 (8.20) | 131 (13.1) | 0.0026 | NS | 0.59 (0.42–0.83) |
| | TT | 2 (0.30) | 2 (0.2) | 0.65 | NS | 1.58 (0.22–11.24) |
| | G | 1147 (95.60) | 1865 (93.30) | | | Reference |
| | T | 53 (4.40) | 135 (6.8) | 0.0066 | NS | 0.64 (0.46–0.88) |
| rs947474 | AA | 379(63.17) | 686 (68.60) | | | Reference |
| | AG | 204 (34.00) | 287 (28.70) | 0.024 | NS | 1.29 (1.03–1.60) |
| | GG | 17 (2.83) | 27 (2.70) | 0.68 | NS | 1.14 (0.61–2.12) |
| | A | 962 (80.17) | 1659 (82.95) | | | Reference |
| | G | 238 (19.83) | 341 (17.05) | 0.048 | NS | 1.20 (1.00–1.45) |
| rs842647 | GG | 456 (76.00) | 759 (75.90) | | | Reference |
| | GA | 135 (22.50) | 222 (22.20) | 0.92 | NS | 1.01 (0.79–1.29) |
| | AA | 9 (1.50) | 19 (1.90) | 0.56 | NS | 0.79 (0.35–1.76) |
| | G | 1047 (87.25) | 1740 (87.00) | | | Reference |
| | A | 153 (12.75) | 260 (13.00) | 0.84 | NS | 0.98 (0.79–1.21) |
| rs702873 | GG | 418 (69.67) | 732 (73.20) | | | Reference |
| | AG | 165 (27.50) | 241 (24.10) | 0.12 | NS | 1.20 (0.95–1.51) |
| | AA | 17 (2.83) | 27 (2.70) | 0.76 | NS | 1.10 (0.59–2.05) |
| | G | 1001 (83.42) | 1705 (85.25) | | | Reference |
| | A | 199 (16.58) | 295 (14.75) | 0.17 | NS | 1.15 (0.94–1.40) |
| rs13031237 | GG | 570 (95.00) | 962 (96.20) | | | Reference |
| | GT | 27 (4.50) | 38 (3.80) | 0.48 | NS | 1.20 (0.72–1.99) |
| | TT | 3 (0.50) | 0 (0) | 0.025 | NS | 2.69 (2.52–2.87) |
| | G | 1167 (97.25) | 1962 (98.10) | | | Reference |
| | T | 33 (2.75) | 38 (1.90) | 0.11 | NS | 1.46 (0.91–2.34) |

$P_c$-Bonferroni-corrected p value; CI-confidence interval; OR-odds ratio; NS-not significant; SNP-single nucleotide polymorphism.

randomly enrolled from the whole population of patients and healthy controls, to identify the susceptible SNPs ($P_c$<0.05). The results demonstrated that the frequencies of the GC genotype and the C allele of rs4750316 were statistically significantly decreased in patients with VKH syndrome compared with controls (GC genotype: Bonferroni-corrected P value ($P_c$)=6.00e-5, odds ratio [OR]=0.44, 95% confidence interval [CI]=0.31–0.62; C allele: $P_c$=1.12e-4, OR=0.47, 95% CI=0.34–0.65). No statistically significant difference was observed in the genotype or allele frequencies of rs11258747, rs947474, rs842647, rs702873, and rs13031237 between patients with VKH syndrome and healthy controls ($P_c$>0.05).

In the second-stage study, we replicated the association of the rs4750316 polymorphism using another set of 259 patients with VKH syndrome and 542 controls. Genotype distribution and allele frequencies are shown in Table 4. The results showed a statistically significantly reduced frequency of the GC genotype and the C allele in patients with VKH syndrome when the GG genotype and the C allele were used as a reference ($P_c$=7.75e-5; $P_c$=0.0002, respectively).

Table 4. Frequencies of alleles and genotypes *PRKCQ* polymorphisms in patients and controls in the second stage and combined results

| SNP | Genotype allele | Second-stage | | | | Meta-analysis | |
|---|---|---|---|---|---|---|---|
| | | Cases (n=259) | Controls (n=542) | *P* value (OR, 95% CI) | $P_c$ | *P* value | (OR, 95% CI) |
| rs4750316 | GG | 246 (94.98) | 451 (83.21) | | | | Reference |
| | GC | 12 (4.63) | 88 (16.24) | 3.23e-6 (OR=0.25, 95% CI= 0.13–0.47) | 7.75e-5 | 2.45e-10 | (OR=0.37, 95% CI= 0.28–0.51) |
| | CC | 1 (0.39) | 3 (0.55) | 0.67 (OR=0.61, 95% CI= 0.063–5.91) | NS | 0.47 | (OR=0.61, 95% CI= 0.16–2.30) |
| | G | 504 (97.30) | 990 (91.32) | | | | Reference |
| | C | 14 (2.70) | 94 (8.67) | 8.32e-6 (OR=0.29, 95% CI= 0.16–0.52) | 0.0002 | 8.79e-10 | (OR=0.41, 95% CI= 0.31–0.55) |

$P_c$-Bonferroni-corrected p value; CI-confidence interval; OR-odds ratio; NS-not significant; SNP-single nucleotide polymorphism.

The combined results of the first- and second-stage studies using meta-analysis also showed a statistically significant association of SNP rs4750316 between the syndrome and healthy controls when the GG genotype or the G allele was used as the reference (GC genotype: *P*=2.45e-10, OR=0.37, 95% CI=0.28–0.51; C allele: *P*=8.79e-10, OR=0.41, 95% CI=0.31–0.55).

The relationship between the six SNPs and clinical features of VKH syndrome, including headache, alopecia, poliosis, vitiligo, tinnitus, neck stiffness, dysacusia, and scalp hypersensitivity, was then analyzed. The frequencies of the C allele of rs4750316 *PRKCQ* were statistically significantly lower in patients with headache, alopecia, poliosis, tinnitus, and dysacusia than in controls when the G allele was used as the reference ($P_c$=6.96e-5, OR=0.38, 95% CI=0.25–0.57 ; $P_c$=0.0011, OR=0.43, 95% CI=0.28–0.65; $P_c$=6.74e-4, OR=0.41, 95% CI=0.27–0.63; $P_c$=4.32e-4, OR=0.44, 95% CI=0.30–0.65; $P_c$=0.013, OR=0.48, 95% CI=0.31–0.73; respectively; Table 5). A statistically significant relationship among the other five SNPs was not observed between patients with VKH syndrome and the clinical manifestations and controls.

## DISCUSSION

The present two-stage study investigated the association of *PRKCQ* polymorphisms (rs4750316, rs11258747, and rs947474) and *REL* polymorphisms (rs842647, rs702873, and rs13031237) with VKH syndrome in a Han Chinese cohort. The results demonstrated that the frequencies of the GC genotype and the C allele of rs4750316 were negatively correlated with patients with VKH syndrome in this Han Chinese cohort. An association with VKH syndrome of the two tested SNP polymorphisms (rs11258747 and rs947474) in the *PRKCQ* gene or the three tested SNP polymorphisms (rs842647, rs702873, and rs13031237) in the *REL* gene in the Han Chinese cohort was not found.

We made the following efforts to control quality. First, exclusion of non-Han individuals was performed to avoid interference from different genetic ancestries, and the distribution of variants in cases and controls was in accordance with HWE. In addition, the patients were diagnosed strictly following the previously described criteria. Then, to confirm the genotype results with PCR-RFLP, 10% of the samples were randomly chosen for sequencing, and the two results were absolutely in line.

The rs4750316 polymorphism in the *PRKCQ* gene was first identified as a susceptibility locus in Caucasians with RA, and subsequently, reported to have no association with BD in the Chinese Han population [27,35]. In this study, three SNPs of *PRKCQ* were genotyped. In one of these SNPs, rs4750316, a negative association between the GC genotype and the C allele with VKH syndrome was observed, suggesting that the rs4750316 C allele is a common protective factor for VKH syndrome and RA. Whether the observed rs4750316 polymorphism influences the underlying biologic function of *PRKCQ* remains unclear, and deserves further investigation. Regarding the two other tested SNPs, rs11258747 and rs947474, in the *PRKCQ* gene, no association

with patients with VKH syndrome in the Han Chinese population was detected, although an association with T1DM in British cohorts was reported [32,36]. In the case of another selected *REL* gene, associations between rs842647 GG and potential CD in populations of southern Italy and BD in Han Chinese populations have been observed [27,37]. Previous studies reported that the SNP rs13031237 T allele was associated with RA in the British population, and with systemic lupus erythematosus (SLE) in a Chinese cohort [38,39], and an association between the rs702873 G allele and psoriasis in the United Kingdom (UK) and Ireland has previously been observed [40]. However, no association was observed between the SNPs rs842647, rs13031237, and rs702873 in *REL,* and susceptibility to VKH syndrome in the Han Chinese population. These differences in genetic models involving VKH syndrome, BD, RA, SLE, and psoriasis may be attributable to heterogeneous genetic loci, distinct environmental exposures, or different ethnic populations, which may lead to distinct underlying pathogenic mechanisms.

The association between the extraocular clinical findings in patients with *PRKCQ* and *REL* polymorphisms was also investigated. The extraocular findings included headache, alopecia, poliosis, vitiligo, tinnitus, stiffness, dysacusia, and scalp hypersensitivity. The rs4750316 C allele was associated with a reduced risk of headache, alopecia, poliosis, tinnitus, and dysacusia in patients with VKH syndrome. These findings show that the *PRKCQ* rs4750316 polymorphism is associated not only with the occurrence of disease but also with the clinical findings of disease. No association between any of the other five tested SNP polymorphisms or clinical characteristics of patients was observed.

VKH syndrome is generally defined as a multisystemic inflammatory disease caused by a T-cell-mediated autoimmune dysfunction targeting melanocytic self-antigens. In addition to mediating the key costimulatory CD28 signal, the *PRKCQ* gene, encoding PKC-θ, activates the NF-κB signaling pathway [41]. The present study showed that the *PRKCQ* gene was associated with VKH syndrome susceptibility, whereas the *REL* gene was not, suggesting that the TCR signaling pathway gene, *PRKCQ*, and not the NF-κB signaling gene, *REL*, plays a crucial role in VKH syndrome pathogenesis.

There are some limitations in this study. The results identified the relationship between the variants in the *PRKCQ* and *REL* genes and patients with VKH syndrome from a Han Chinese cohort. Therefore, other ethnic groups must be replicated in future studies. Furthermore, the biologic role of the observed *PRKCQ* rs4750316 polymorphism in relation to VKH syndrome pathogenesis remains unknown. The fact that *PRKCQ* has a risk effect on the pathogenesis of VKH syndrome may provide an attractive therapeutic strategy for management of this disease.

Collectively, the results of this study showed that *PRKCQ* rs4750316 may point to a predisposition to VKH syndrome, and that *PRKCQ* may be involved in the pathogenesis and

**Table 5. Frequencies of alleles and genotypes of rs4750316/*PRKCQ* polymorphisms in patients with clinical findings and controls**

| Allele | Clinical findings | Cases | Controls | *P* value | $P_c$ | OR (95% CI) |
|---|---|---|---|---|---|---|
| | **Headache** | **n=364** | **n=1542** | | | |
| G | | 704 (96.70) | 2827 (91.66) | | | Reference |
| C | | 24 (3.30) | 257 (8.33) | 2.90e-6 | 6.96e-5 | 0.38 (0.25–0.57) |
| | **Alopecia** | **n=334** | **n=1542** | | | |
| G | | 643 (96.26) | 2827 (91.67) | | | Reference |
| C | | 25 (3.74) | 257 (8.33) | 4.50e-5 | 0.0011 | 0.43 (0.28–0.65) |
| | **Poliosis** | **n=332** | **n=1542** | | | |
| G | | 640 (96.39) | 2827 (91.67) | | | Reference |
| C | | 24 (3.61) | 257 (8.33) | 2.81e-5 | 6.74 e-4 | 0.41 (0.27–0.63) |
| | **Tinnitus** | **n=400** | **n=1542** | | | |
| G | | 769 (96.13) | 2827 (91.67) | | | Reference |
| C | | 31 (3.87) | 257 (8.33) | 1.80e-5 | 4.32e-4 | 0.44 (0.30–0.65) |
| | **Dysacusia** | **n=289** | **n=1542** | | | |
| G | | 554 (95.85) | 2827 (91.67) | | | Reference |
| C | | 24 (4.15) | 257 (8.33) | 0.00053 | 0.013 | 0.48 (0.31–0.73) |

$P_c$-Bonferroni-corrected p value; CI-confidence interval; OR-odds ratio; NS-not significant.

clinical manifestations of VKH syndrome. No association between any of the other tested SNPs with VKH syndrome in the Han Chinese cohort was detected.

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