Research Paper

**BARD1 Gene Polymorphisms Confer Nephroblastoma Susceptibility**

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**A B S T R A C T**

BRCA1-associated RING domain protein 1 (BARD1) is a tumor suppressor, which forms a heterodimer with BRCA1. Three BARD1 gene polymorphisms (rs7585356 G→A, rs6435862 T→G and rs768716 A→G) were initially identified as high-risk nephroblastoma susceptibility loci by a previous GWAS. Because of the general tumor-suppressing function of BARD1, we hypothesized that these BARD1 gene polymorphisms might modify the susceptibility to nephroblastoma. We genotyped these polymorphisms in 145 cases and 531 controls using Taqman methods. Out of three polymorphisms, only the rs7585356 G→A polymorphism was significantly associated with increased susceptibility to nephroblastoma [AA vs. GG: adjusted odds ratio (OR) = 1.78, 95% confidence interval (CI) = 1.01–3.12]. Combined analysis of three polymorphisms indicated that subjects with 3 risk genotypes exhibited significantly elevated nephroblastoma risk, when compared with subjects with 0–2 risk genotypes [adjusted OR = 1.72, 95% CI = 1.02–2.89]. Stratified analysis revealed that in terms of clinical stage, rs7585356 AA carriers were associated with increased risk of developing clinical stage I + II nephroblastoma. The presence of three risk genotypes was significantly associated with nephroblastoma risk in females and clinical stage I + II nephroblastoma. Our results suggested that BARD1 rs7585356 G→A may be associated with nephroblastoma risk.

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1. Introduction

Nephroblastoma (Wilms' tumor) is an embryonal kidney malignancy. It is the most commonly diagnosed renal tumor in children, but rarely occurs in adults. The annual incidence rate of nephroblastoma is about 7–10 cases per 100,000 children younger than 15 years old, making up 6–7% of all childhood cancers (Ko and Ritchey, 2009). The incidents vary among the different ethnic groups, with the highest rates found in black Africans and the lowest in Asians (Ko and Ritchey, 2009). The variation in incident rates reflected implication of genetic factors in the etiology of the disease. It was estimated that nephroblastoma affected 3.3 in one million children between 2002 and 2010 in China (Bao et al., 2013). Nephroblastoma is highly responsive to treatments, with a relatively favorable prognosis. The long-term survival for regional and metastatic disease is over 90% and 75%, respectively (Ko and Ritchey, 2009; Szychot et al., 2014). However, there is still room for improvement in risk prediction and management of the disease.

Approximately, 10%–15% of nephroblastomas are related to germline pathogenic variants or epigenetic alterations formed in the early stage of embryogenesis (Dome and Huff, 1993). Roughly 1%–2% of cases have at least one relative also developed Wilms' tumor. Germline genetic and epigenetic variations are most frequently identified in Wilms' Tumor 1 (WT1) gene and the 11p15.5 locus (Dome and Huff, 1993) in patients with Wilms' tumor. In addition, genetic aberrations in other genes, including VHL, BRFM1, BAP1, may be implicated in the tumorigenesis of kidney cancers (Tan et al., 2015). Although pathogenic genetic alterations are clear in some families, they remain unknown for the majority of individuals. Therefore, additional relevant variants in other genes should be further explored.

BRCA1-associated RING domain protein 1 (BARD1) is encoded by the human BARD1 gene, which is known to interact with breast cancer
susceptibility gene 1 (BRCA1) [ Wu et al., 1996; Irminger-Finger and Jefford, 2006; Irminger-Finger et al., 2016]. BARD1 shares homologies with BRCA1 in primary structure within the N-terminal RING finger motif and two C-terminal BRCA1 carboxy-terminal (BRCT) domains (Wooster et al., 1994). These two proteins form a heterodimer through their N-terminal RING finger motifs (Meza et al., 1999). BARD1 is able to regulate the tumor-suppressor function of BRCA1 (Greenberg et al., 2006; Kim et al., 2006; Simons et al., 2006; Irminger-Finger et al., 2016). Disruption of the BARD1/BRCA1 interaction may impair BRCA1 tumor suppression functions. BARD1 itself is also a tumor suppressor (Irminger-Finger et al., 2016). Mice with conditional deletion of BARD1 in mammary epithelial cells developed breast cancer (Shakya et al., 2008). Moreover, structure-affecting mutations in the BARD1 gene were frequently identified in breast, ovarian, and uterine cancers (Irminger-Finger and Jefford, 2006). Because of the biological importance of BARD1, single nucleotide polymorphisms (SNPs) that alter its function or expression may modify susceptibility to cancer. A previous genome-wide association study (GWAS) found that BARD1 gene polymorphisms (rs7585356 G→A, rs6435862 T→G and rs3768716 A→G) were associated with nephroblastoma susceptibility (Capasso et al., 2009). Given the importance of BARD1 in cancer, we investigated whether the three SNPs confer nephroblastoma susceptibility in a Southern Chinese population consisting of 145 cases and 531 controls.

2. Materials and Methods

2.1. Study Population

Totally, 145 patients with nephroblastoma and 531 cancer-free controls were recruited for this hospital-based case-control study. All the cases were enrolled from the Guangzhou Women and Children’s Medical Center, with newly diagnosed and histopathologically verified nephroblastoma. The cancer-free controls were frequency matched to cases on age and sex, who visited the same hospital for a regular physical examination (He et al., 2016a,b,c,d; Zhang et al., 2016; Zheng et al., 2016). All the participants were ethnic Chinese Han. Patients would be excluded, if bearing other types of tumor, secondary or recurrent tumors, and receiving chemotherapy or radiotherapy previously. Demographic and clinical data on each participant, including age, sex, and clinical characteristics, were acquired by structured questionnaire or archived medical records. This study obtained approval from the Institutional Review Board of Guangzhou Women and Children’s Medical Center. Written informed consent was signed by all participants or their guardians in accordance with the Declaration of Helsinki.

2.2. SNP Selection and Genotyping

Three SNPs (rs7585356 G→A, rs6435862 T→G, and rs3768716 A→G) in the BARD1 gene identified in a previous GWAS were chosen for this study (Capasso et al., 2009). We used the TIANamp Blood DNA Kit (TianGen Biotech Co., Ltd., Beijing, China) to isolate genomic DNA from 2 mL venous blood sample, following the manufacturer’s instructions (He et al., 2016c). Samples of genomic DNA were processed according to previous protocol (He et al., 2012; Zhu et al., 2015, 2016). Generally, we prepared all the DNA samples in a dilution of 10 ng/μL and added to the 96-well plates until further utilization. Genotyping for the SNPs was performed in the 384-well format and Taqman method was adopted. For the purpose of quality control, 10% of samples were picked randomly and regenotyped, and the two sets of genotyping results were 100% concordant.

2.3. Statistical Analysis

χ² test was performed to compare the differences in the demographic variables and distributions of genotypes between cases and controls. We used goodness-of-fit χ² test to evaluate whether genotype distributions of SNPs followed Hardy-Weinberg equilibrium (HWE) in control subjects. Unconditional univariate logistic regression analysis was performed. Furthermore, odds ratios (ORs) and 95% confidence intervals (CIs), with adjustment for age and sex, were computed to determine the strength of the associations between studied SNPs and the risk of nephroblastoma. We also performed false-positive report probability (FPRP) analysis to further explore if the significant findings were just chance or noteworthy observations (He et al., 2016a). SAS software (version 9.1; SAS Institute, Cary, NC) was used to conduct all statistical analyses. All P values were two-sided, and a significance level of 0.05 was adopted for this study.

3. Results

3.1. Characteristics of Study Population

We totally recruited 145 nephroblastoma patients and 531 cancer-free controls with ages ranging from 1 to 156 months old, respectively (Table 1). There were no significant differences between cases and controls regarding age (P = 0.725) and sex (P = 0.956). The clinical stages were also obtained for nephroblastoma patients. There were 4 patients (2.76%) in stage I, 49 (33.49%) in stage II, 50 (34.48%) in stage III, and 33 (22.76%) in stage IV. We failed to determine clinical stage for 9 patients.

3.2. Association Analysis

We performed the goodness-of-fit χ² test to test whether the distribution of genotype frequency of SNPs departed from expected pattern (Table 2). All the P values were above 0.05 (rs7585356 G→A: P_{HWE} = 0.948; rs6435862 T→G: P_{HWE} = 0.205; rs3768716 A→G: P_{HWE} = 0.415) suggested that all the analyzed SNPs were in accordance with HWE in the control subjects. Single locus analysis demonstrated that the rs7585356 G→A polymorphism was significantly associated with an increased risk of nephroblastoma (AA vs. G: adjusted OR = 1.78, 95% CI = 1.01–3.12). There was no association observed for either the rs6435862 T→G or the rs3768716 A→G polymorphism. We next examined the combined effects of risk genotypes. There was a trend showing that the risk of nephroblastoma was increasing with the number of risk genotypes (adjusted OR = 1.26, 95% CI = 1.03–1.53). However, only carriers of three risk genotypes were at significantly higher risk than those without risk genotype (adjusted OR = 2.21, 95% CI = 1.18–4.17). Moreover, when we divided subjects into two groups (0–2 and 3 risk genotypes), we found that subjects with 3 risk genotypes

| Variables | Cases (n = 145) | Controls (n = 531) | P* |
|-----------|----------------|-------------------|----|
| Age range, month | 1–132 0.07–156 0.725 | | |
| Mean ± SD | 26.17 ± 21.48 29.73 ± 24.86 | | |
| ≤18 | 68 45.52 233 43.88 | | |
| >18 | 79 54.48 298 56.12 | | |
| Gender | Female 0.956 Male | | |
| 64 44.14 233 43.88 | | |
| 81 55.86 298 56.12 | | |
| Clinical stages | I 2.76 | | |
| II 49 33.79 | | |
| III 50 34.48 | | |
| IV 33 22.76 | | |
| NA 9 6.21 | | |

* Two-sided χ² test for distributions between nephroblastoma cases and cancer-free controls.
exhibited significantly elevated nephroblastoma risk in comparison to subjects with 0–2 risk genotypes (adjusted OR = 1.72, 95% CI = 1.02–2.89).

3.3. Stratified Analysis

We then performed stratified analysis to explore how age, gender, and clinical stage influence the association between selected polymorphisms and nephroblastoma susceptibility (Table 3). No association was observed between individual SNPs and nephroblastoma susceptibility in subgroups defined by age and sex. Interestingly, we found that subjects carrying rs7585356 AA genotype significantly tended to develop clinical stage I + II nephroblastoma, when compared with those carrying G alleles. However, the rs7585356 AA genotype did not appear to increase the risk of clinical stage III + IV nephroblastoma. We further investigated the cumulative effects of these SNPs on nephroblastoma in the stratified analysis. We found that the presence of three risk genotypes was significantly associated with the risk of nephroblastoma.

Table 3
Stratification analysis for association between BARD1 genotypes and nephroblastoma risk.

| Variables | rs7585356 (case/control) | rs6435862 (case/control) | rs3768716 (case/control) | Risk genotypes (case/control) |
|-----------|--------------------------|--------------------------|--------------------------|-------------------------------|
| Genotype  | Adjusted ORa (95% CI)    | Adjusted ORa (95% CI)    | Adjusted ORa (95% CI)    | Adjusted ORa (95% CI)          |
|           | AA/AG                   | TT/TC                    | TG/TC                    | 0–2                           |
| Age, month | s18                      | >18                      | Gender                   | Male                          |
|           | 56/205                  | 11/28                    | 22/102                   | 65/626                      |
|           | 1.69 (0.81–3.55)        | 1.82 (0.79–3.32)         | 2.88 (0.97–4.46)         | 3.92 (0.65–2.69)             |
|           | 0.165 (49/167) 15/66    | 0.193 (63/214) 14/84     | 0.060 (52/160) 12/73     | 0.441 (60/221) 17/77         |
|           | 0.78 (0.41–1.48)        | 0.36 (0.30–1.05)         | 0.51 (0.26–1.01)         | 0.80 (0.44–1.46)             |
|           | 0.447 (47/154) 17/79    | 0.070 (61/210) 16/88     | 0.054 (49/150) 13/83     | 0.474 (59/214) 18/84         |
|           | 0.71 (0.38–1.32)        | 0.61 (0.33–1.12)         | 0.55 (0.29–1.05)         | 0.76 (0.43–1.37)             |
|           | 0.277 (52/206) 12/27    | 0.110 (65/269) 12/29     | 0.070 (52/211) 12/22     | 0.369 (65/264) 12/34         |
|           | 1.77 (0.84–3.73)        | 1.74 (0.84–3.61)         | 2.19 (1.01–4.71)         | 1.42 (0.70–2.90)             |
|           | s18                      | >18                      | Gender                   | Male                          |
| Clinical stage | I + II 40/472 | 11/59                    | 21.4 (1.03–4.45)         | 0.041 (41/381) 10/150         |
|           | 0.019 (41/364) 10/167   | 0.62 (0.30–1.27)         | 0.62 (0.30–1.27)         | 0.63 (0.35–1.12)             |
|           | 2.29 (1.10–4.77)        | 2.29 (1.10–4.77)         | 1.79 (1.01–4.71)         | 1.42 (0.70–2.90)             |

The results were in bold if the 95% CI excluded 1 or P < 0.05.

a Adjusted for age and gender.
nephroblastoma in females when compared with that of 0–2 risk genotypes (adjusted OR = 2.19, 95% CI = 1.01–4.71). Moreover, carriers of three genotypes had 2.29-fold increase in the risk of developing clinical stage I + II nephroblastoma (95% CI = 1.10–4.77).

Thus, when we performed FPRP analysis, all the significant findings disappeared at the prior probability level of 0.1 and FPRP threshold of 0.2 (Table 4).

### 4. Discussion

Genetic factors have been known to contribute to the development of nephroblastoma. However, genetic factors related to nephroblastoma are largely unknown, except for some genetic and epigenetic alterations in WT1 and the 11p15.5 locus (Dame and Huff, 1993). Previous GWAS initially discovered six BARD1 SNPs significantly associated with high-risk nephroblastoma susceptibility (Capasso et al., 2009). We tested the rs6435862 T→G, rs3768716 A→G, and rs7585356 G→A, because the rs6435862 T→G and rs3768716 A→G were the most significant SNPs in that GWAS study, and the last one is positioned in the 3′ UTR region. Another reason why we studied these SNPs was due to the importance of BARD1 in cancer. These three SNPs were also chosen for our previous replication study in Southern Chinese population with 201 nephroblastoma patients and 531 controls (Zhang et al., 2016).

In this study, we investigated the roles of three polymorphisms in the BARD1 gene in modifying nephroblastoma susceptibility in this case-control study with 145 nephroblastoma patients and 531 controls. Among the three SNPs, only the rs7585356 G→A polymorphism was significantly associated with nephroblastoma susceptibility. Intriguingly, stratified analysis indicated that subjects harboring the rs7585356 A allele were more likely to have early stage of the disease. The rs7585356 AA homozygotes had a significantly increased risk of nephroblastoma at OR of 1.78. Moreover, these SNP might collectively contribute to the risk. The risk of developing nephroblastoma for subjects with three risk genotypes was significantly higher than those carrying two risk genotypes or less. Moreover, in the stratified analysis, the significant association was observed in females and patients with stage I and II disease. Despite the significant findings in the present study, it is should be noted that our previous study reported that based link disequilibrium (LD), these three SNPs could also secure 10 more polymorphisms, using SNPInfo software (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm) (Zhang et al., 2016). The rs3768716 was in LD with rs17487792, rs17488049, rs2070096, while rs7585356 was in LD with rs6435862, rs12614960, 1374230, 16852600, 1979028, and rs207562. As a result, it remain unclear which SNP exactly modifies the risk of nephroblastoma, rs7585356 or another SNP in high LD with it. Moreover, the underlying mechanism by which the significant SNP alters the expression or function of BARD1 needs to be clarified.

Table 4

| Genotype          | Crude OR (95% CI) | P* | Statistical power | Prior probability | 0.25 | 0.1 | 0.01 | 0.001 | 0.0001 |
|-------------------|------------------|----|------------------|------------------|------|-----|------|-------|--------|
| rs7585356 G→A     |                  |    |                  |                  |      |     |      |       |        |
| AA vs. GG         | 1.80 (1.03–3.16) | 0.039 | 0.307 | 0.276 | 0.534 | 0.927 | 0.992 | 0.999 |        |
| AA vs. GG/AG      |                  |    |                  |                  |      |     |      |       |        |
| Stage I + II      |                  |    |                  |                  |      |     |      |       |        |
| Risk genotypes    |                  |    |                  |                  |      |     |      |       |        |
| 3 vs. 0           | 2.24 (1.19–4.21) | 0.012 | 0.175 | 0.175 | 0.388 | 0.875 | 0.986 | 0.999 |        |
| 3 vs. 0–2         | 1.74 (1.04–2.92) | 0.037 | 0.289 | 0.275 | 0.533 | 0.926 | 0.992 | 0.999 |        |
| Females           | 2.21 (1.03–4.76) | 0.042 | 0.161 | 0.440 | 0.702 | 0.963 | 0.996 | 1.000 |        |
| Stage I + II      | 2.33 (1.13–4.80) | 0.022 | 0.122 | 0.347 | 0.614 | 0.946 | 0.994 | 0.999 |        |

*χ² test was used to calculate the genotype frequency distributions.
* Statistical power was calculated using the number of observations in the subgroup and the OR and P values in this table.

Bard1 is lethal in mouse (McCarthy et al., 2003). The study of Bard1 knockout mice demonstrated that BARD1 is indispensable to maintain cell viability and genetic stability (McCarthy et al., 2003). Conditional knockout Bard1 in mammary epithelia cells induced the development of breast cancer, which mimics the human breast cancer phenotype observed in individuals, harboring BRCA1 mutation (Shakya et al., 2008). Mechanistic studies indicated that the BARD1-BRCA1 heterodimer is also implicated in ubiquitin dependent protein degradation as an E3 ubiquitin ligase (Hashizume et al., 2001). Mutations that impaired the E3 ubiquitin ligase activity of the heterodimer predispose to breast and ovarian cancer (Brazovic et al., 2001; Hashizume et al., 2001; Ruffner et al., 2001).

Moreover, some non-synonymous polymorphisms (e.g., cys557Ser, Arg378Ser, Val507Met, and Pro24Ser) in the BARD1 gene have been also frequently investigated for their association with cancer susceptibility, and studies mainly involved breast cancer (Morris et al., 2006; Onay et al., 2006; Stacey et al., 2006; Vahteristo et al., 2006; Guenard et al., 2008; Ding et al., 2011; Sun et al., 2012), nephroblastoma (Capasso et al., 2009, 2013), and cervical cancer (Zhou et al., 2009). Nonetheless, the associations between these BARD1 SNPs and cancer susceptibility have been often paradoxical. Some studies supported the associations (Hu et al., 2007), while others had opposite results (Liu et al., 2015). The factors that contribute to the inconsistency are, but not limited to differences in genotyping methods, experiment designs (hospital-based design or population-based design), different populations and ethnicities, as well as sample size of studies. Therefore, it is critical that all association studies consider external validity issues and candidly state the populations to which the results can be applied. Several meta-analyses were undertaken to reevaluate such associations (Ding et al., 2011; Liu et al., 2015). Ding et al. reported a lack of association between BARD1 Cys557Ser polymorphism and breast cancer risk in a pooled analysis comprising 11,870 cases and 7687 controls in 2011 (Ding et al., 2011). Liu et al. collected 10 case-control studies in 2015 (Liu et al., 2015). They found that BARD1 Val507Met and Pro24Ser polymorphisms were associated with decreased cancer risk independently, but not BARD1 Arg378Ser (Liu et al., 2015).

A number of limitations of this study should be noted. First, owing to the extremely low incidence of nephroblastoma, the sample size of this case-control was relatively small. Consequently, statistic power of this study was compromised (statistical power no more than 0.307 for significant findings). The significant findings might be chance observations (PPR values larger than 0.2 at the prior probability level of 0.1). Second, we concentrated on only three BARD1 SNPs. BARD1 gene is highly polymorphic, harboring 4941 SNPs as a minimum (http://www.ncbi.nlm.nih.gov/projects/SNP). Other SNPs that potentially affect the expression and function of BARD1 should be investigated in the future. Third, we only included Southern Chinese Children in this study. These findings cannot be generalized from one ethnicity to another before validation study. Fourth, in this retrospective study, some important information (e.g., parental exposures) was not available. Due to differences in genetic backgrounds and environmental exposures among the different ethnicities, these findings should be cross-validated with different populations.
Notwithstanding these limitations, our findings did suggest that the rs7585356 G->A polymorphism may confer genetic susceptibility to nephroblastoma. The studied SNPs collectively may increase the risk of nephroblastoma. Moreover, these SNPs appear to be related to the clinical stages of this disease. Well-designed, large, multi-center studies are warranted to strengthen these findings.

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Conflict of Interest Disclosures
The authors declare no competing financial interests.

Authorship Contributions
W. Fu, J. Zhu, J. He and G.C. Liu designed and performed the study; W. Jia, Z. Zhao, S.B. Zhu, J.H. Hu, F.H. Wang and H. Xia collected the samples and information; S.W. Xiong and J. He participated in analyzing data; W. Fu, J. He and G.C. Li coordinated the study over the entire time. All authors reviewed the final manuscript.

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