Association Between BAK1 Gene rs210138 Polymorphisms and Testicular Germ Cell Tumors: A Systematic Review and Meta-Analysis

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Background: Several studies including some genome-wide association studies (GWAS) had shown that BAK1 gene rs210138 polymorphisms might be associated with testicular germ cell tumors (TGCT). Here we tried to sum up the association through a systematic review and meta-analysis.

Methods: Studies associated with BAK1 rs210138 and TGCT was systematically searched in databases. The effect size was pooled according to ORs and 95% CIs.

Results: Our systematic review and meta-analysis comprised 14 articles. Significantly increased risk of TGCT was found in eligible GWAS and follow-up studies, in overall group and its Caucasian subgroup.

Conclusions: Compared with adenine (A), BAK1 rs210138 guanine (G) is associated with increased risk of TGCT. Well-planned studies with larger sample size and more subgroups are needed to verify the risk identified in our systematic review and meta-analysis.

Keywords: BAK1, rs210138, single nucleotide polymorphisms, testicular germ cell tumors, meta-analysis

BACKGROUND

More than 90% of cancers of the testicle develop in germ cells. Testicular germ cell tumor (TGCT) mainly consist of seminomas and non-seminomas (1). The protein encoded by BCL2 antagonist/killer 1 (BAK1) gene belongs to the BCL2 protein family. BAK1 protein localizes to mitochondria, and functions to promote apoptosis. In a kind of Bak−/− mice, 60% mice harbored high-grade tumors within the testis (2). Several studies including some genome-wide association studies (GWAS) (3) had shown that BAK1 gene rs210138 polymorphisms might be associated with TGCT. Here we tried to sum up the association through a systematic review and meta-analysis.
METHODS
Identification of Eligible Studies
Independently, two researchers systematically searched these databases: GWAS Catalog, Wanfang, CNKI, clinicaltrials.gov, Cochrane Library, PubMed, Embase. Term “rs210138” was used in GWAS Catalog. And in other databases, these terms were used without limitation: “BAK1” AND “cancer of testis OR carcinoma of testis OR testicular cancer OR testis cancer OR ball cancer OR testicular germ cell tumors OR TGCT” AND “polymorphisms OR polymorphism.” The last search update was on Nov 30, 2018. For additional studies, we made a manual search in reviews and references of related studies.

Inclusion and Exclusion Criteria
Independently, two researchers made the selection according to the following inclusion criteria: (1) evaluation of the association between BAK1 rs210138 and TGCT susceptibility; (2) case-control study; (3) studies focusing on tissues of human beings; (4) elaborate genotype data in non-GWAS study or enough data in GWAS study could be acquired. Exclusion criteria: (1) duplication of previous publications (When there were multiple publications from the same population, only the largest study was included); (2) review, comment, and editorial; (3) study without enough data; (4) studies focusing on cell lines. Dissertation thesis were included in the analysis. We took experience and inspiration from the article we have published recently (4), in which the inclusion and exclusion criteria was mature and rigorous.

Data Extraction
Data of the eligible studies were extracted by two investigators independently. Conflict was solved by discussion. The third investigator would be involved if necessary. Try to get detailed genotype data by contacting the author.

The following contents were collected: year of publication, the characteristics of cases and controls, first author's surname, ethnicity, Hardy-Weinberg equilibrium, source of control groups, country of origin, genotyping method, number of cases, and controls.

Methodological Quality Assessment
According to Newcastle-Ottawa Scale (NOS) (5), two investigators evaluated qualities of included studies independently. Quality scores range from 0 to 10, and higher scores means better quality of the study. The most important factor was “age, gender, and country.” Conflict was solved by discussion.

Statistics Analysis
This meta-analysis complied with the PRISMA checklists (6). Pooled ORs and 95% CIs were calculated to evaluate the strength of the association between BAK1 gene rs210138 polymorphisms and TGCT susceptibility. Evaluation of Hardy-Weinberg equilibrium (HWE), OR and 95% CIs, heterogeneity, sensitivity, and publication bias were performed according to methods in our published article (4). In addition, I–V random effects model was used in total to get all data shown in Table 4 except overall subgroup. Sensitivity analyses and...
| No. | Study ID | Year | Country or area | Ethnicity | Control type | Genotyping method | Case | Control | P for HWE* | Quality |
|-----|----------|------|----------------|-----------|--------------|------------------|------|----------|------------|---------|
| 1.1 | Poynter et al.* (7) | 2012 | USA | Caucasian | PB* | Sequencing | 3 | 4 | 8 | 6 | 16 | 57 | 0.007* | 6 |
| 1.2 | Lessel et al. (8) | 2012 | Croatia | Caucasian | PB | TaqMan | 30 | 109 | 179 | 43 | 87 | 221 | 0.156 | 8 |
| 1.3 | Duan (9) | 2016 | China | Chinese | PB | Sequencing | 16 | 31 | 29 | 12 | 63 | 73 | 0.756 | 7 |
| 1.3.1 | Duan | 2016 | China | Han | PB | Sequencing | 11 | 16 | 10 | 9 | 40 | 34 | 0.584 | 7 |
| 1.3.2 | Duan | 2016 | China | Uygur | PB | Sequencing | 5 | 15 | 19 | 3 | 23 | 39 | 0.867 | 7 |
| 1.4 | Dantsev et al. (10) | 2018 | Russia | Caucasian | PB | PCR-RFLP | 7 | 53 | 82 | 0 | 50 | 103 | 0.016* | 9 |

Follow up (G vs. A)

| GWAS (G vs. A) | Case/Control, RA*, OR* (95%CI*), P-value | Quality |
|----------------|----------------------------------------|---------|
| 2.1 Kratz et al.* (11) (follow up) | 119/871, G, 1.80 (1.35–2.41), 7.03 × 10^{−5} | FTCS* |
| 2.2 Marcotte et al.* (12) (follow up) | 91 complete case-parent trios, G, 3.31 (1.89–5.79), NA* | CCRN* |

GWAS (G as A)

| Study ID | Year | Country or area | Ethnicity | Control type | Genotyping method | Case | Control | P-value | Quality |
|----------|------|----------------|-----------|--------------|------------------|------|----------|---------|---------|
| 3.1 | Rapley et al. (13) | 2009 | UK | Caucasian | PB | Illumina 370K (cases) | 730/1,435, G, 1.50 (1.30–1.74), 4.5 × 10^{−8} | UKTCC* |
| 3.1.1 | Discovery study (GWAS) | | | | | | 730/1,435, G, 1.50 (1.30–1.74), 4.5 × 10^{−8} | |
| 3.1.2 | Replication study (follow up) | | | | | | 571/1,806, G, 1.50 (1.28–1.75), 6.6 × 10^{−7} | UKTCC |
| 3.2 | Ruark et al. (14) | 2013 | UK | Caucasian | PB | Illumina HumanCNV370Duo (cases) | 986/4,946, G, 1.55 (1.39–1.73), 1.47 × 10^{−14} | UKTCC |
| 3.2.1 | Discovery study (GWAS) | | | | | | | |
| 3.2.2 | Replication study (follow up) | | | | | | 1,327/6,687, G, NA, NA | |
| 3.3 | UKTCC + Sweden/Norway (15) | | | | | | | |
| 3.3.1 | Litchfield et al. (15) (GWAS) | 2017 | UK | Caucasian | PB | Oncoarray platform | 3,206/7,422, G, 1.42 (1.35–1.49), 8.5 × 10^{−22} | UKTCC |
| 3.3.2 | Kristiansen et al. (16) (GWAS) | 2015 | Sweden/Norway | Caucasian | PB | NA (cases) | 1,327/6,687, G, NA, NA | Sweden/Norway |
| 3.3.3 | Ruark et al. (14) (GWAS) | 2013 | UK | Caucasian | PB | as 3.2.1 | 986/4,946, G, 1.55 (1.39–1.73), 1.47 × 10^{−14} | UKTCC |
| 3.4 | NCI (17, 18) (GWAS) | NA | USA | Caucasian | PB | Illumina 660K | 479/555, G, NA, NA | NCI* |
| 3.4.1 | STEED (GWAS) | | | | | | 582/1,056, G, 1.62 (1.35–1.95), 2.83 × 10^{−7} | STEED* |
| 3.4.2 | FTCS (GWAS) | | | | | | 103/501, G, NA, NA | FTCS* |
| 3.5 | NCI + USC (19) | | | | | | | |
| 3.5.1 | Schumacher et al. (19) (GWAS) | NA | USA | Caucasian | PB | Illumina 610K | 358/503, G, NA, NA | USC* |
| 3.6 | Kanetsky et al. (20) (GWAS) | 2011 | USA | Caucasian | PB | As 3.4 | 582/1,056, G, 1.62 (1.35–1.95), 2.83 × 10^{−7} | NCI |
| 3.6.1 | Discovery study (GWAS) | | | | | | 349/914, G, 1.34 (1.08–1.66), 0.0074 | UPENN* |
| 3.6.2 | Replication study (follow up) | | | | | | 397/862, G, 1.23 (0.99–1.52), 0.065 | |

*HWE, Hardy–Weinberg equilibrium; PB, population-based; HB, hospital-based; RA, risk allele; OR, Odds ratio; CI, confidence interval; NA, not available.

*Results with statistical significant difference were marked as bold.

Poynter et al.’s study focused on pediatric GCs with age <22 years at diagnosis, and several extragonadal germ cell tumor male cases were included.

Kratz et al.’s study used generalized estimating equations method to get OR and 95% CIs, and included 97 cases with familial TGCT and 22 cases with sporadic bilateral TGCT.

Marcotte et al.’s study focused on pediatric GCs with age <20 years at diagnosis, included 91 TGCT complete case-parent trios, and used transmission disequilibrium test method to get OR and 95% CIs.

*Detailed in Table 2.
In total, we captured 66 articles from databases (PubMed = 13, Embase = 18, Cochrane = 0, clinicaltrials.gov = 0, CNKI = 22, Wanfang = 3, GWAS Catalog = 5, other sources = 5). Figure 1 displayed the selection process. One full-text article was excluded for not about rs210138. Finally, 14 records (7–20) were included in our systematic review and meta-analysis. Tables 1, 2 displayed characteristics of each study. The control group of study Poynter et al. (7) and Dantsev et al. (10) had shown significant departure from HWE.

### RESULTS

#### Characteristics of Studies

In total, we captured 66 articles from databases (PubMed = 13, Embase = 18, Cochrane = 0, clinicaltrials.gov = 0, CNKI = 22, Wanfang = 3, GWAS Catalog = 5, other sources = 5). Figure 1 displayed the selection process. One full-text article was excluded for not about rs210138. Finally, 14 records (7–20) were included in our systematic review and meta-analysis. Tables 1, 2 displayed characteristics of each study. The control group of study Poynter et al. (7) and Dantsev et al. (10) had shown significant departure from HWE.

#### Meta-Analysis Overall

In overall group and its Caucasian subgroup, significantly increased risk of TGCT was found in all genetic models of BAK1 rs210138 (Table 3 and Figure 2). And the results showed stability in sensitivity analyses in four genetic models (Table 3).

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**TABLE 2** | Characteristics of cases and controls.

| Study ID | Case | Control |
|----------|------|---------|
| Kratz et al. (11) | From NCI Clinical Genetics Branch Familial Testicular Germ Cell Study (FTCS). | From the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial. |
| Marcotte et al. (12) | From the Children’s Oncology Group Childhood Cancer Research Network (CCRN). | Parents of cases. |
| Rapley et al. (13) | From a UK study of familial testicular cancer and a national collection of TGCT Cases treated within the UK. Cases were recruited via the UK Testicular Cancer Collaboration (UKTCC). | From the 1958 Birth Cohort (1958BC). |
| Ruark et al. (14) | From a UK study of familial testicular cancer and a national collection of TGCT Cases treated within the UK. Cases were recruited via the UK Testicular Cancer Collaboration (UKTCC). | Controls for the GWAS: 2,482 from the 1958 Birth Cohort (1958BC) and 2,587 from the UK National Blood Service (NBS). Controls for the iCOGs replication: 814 age <65 male from a study of Prostate Cancer (UKGPCS), 7,871 controls (6,627 female and 1,244 male) from a SEARCH (Study of Epidemiology & Risk Factors in Cancer), 1,397 females from the BBCS (British Breast Cancer Study). |
| Litchfield et al. (15) | From a UK study of familial testicular cancer and a national collection of TGCT Cases treated within the UK. Cases were recruited via the UK Testicular Cancer Collaboration (UKTCC). | Controls of the FTCS. |
| Kristiansen et al. (16) | Recruitment of Norwegian TGCT patients diagnosed between 1990 and 2008 was based on data from the Cancer Registry of Norway. Recruitment of Swedish TGCT patients diagnosed between 1995 and 2006 was based on data from the Swedish National Cancer Registry. | From the TwinGene project, conducted between 2004 and 2008, is a population-based Swedish study of twins born between 1911 and 1958. |
| NCI (17, 18) | From NCI Clinical Genetics Branch Familial Testicular Germ Cell Study (FTCS) and US Servicemen's Testicular Tumor Environmental and Endocrine Determinants Study (STEED). | From the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial and STEED. |
| USC (19) | Individuals analyzed are part of a population-based study at the University of California (USC) based in the California and the California Cancer Registry (CCR). | Controls from the NCI Breast & Prostate Cancer Cohort Consortium genome-wide study of aggressive prostate cancer. |
| Kanetsky et al. (20) | Most cases of discovery study were from the University of Pennsylvania (UPENN) Health System or Fox Chase Cancer Center. Cases of replication study were from western Washington State. | Controls of the NCI Breast & Prostate Cancer Cohort Consortium genome-wide study of aggressive prostate cancer. |

**TABLE 3** | Summary of pooled ORs in the meta-analysis with detailed genotype.

| BAK1 rs210138 | Number (cases/controls) | G vs. A | OR (95% CI) | P (%) | GG vs. AA | OR (95% CI) | P (%) | AG vs. AA | OR (95% CI) | P (%) | AG + GG vs. AA | OR (95% CI) | P (%) | GG vs. AA + AG | OR (95% CI) | P (%) |
|--------------|------------------------|---------|-------------|-------|-----------|-------------|-------|-----------|-------------|-------|----------------|-------------|-------|----------------|-------------|-------|
| Overall      | 551/702                | 1.701   | (1.403–2.062)* | 0.0   | 3.424     | (2.065–5.622) | 0.0   | 1.459     | (1.136–1.876)* | 0.0   | 1.671          | (1.318–2.119) | 0.0   | 2.974          | (1.848–4.786) | 0.0   |
| Caucasian subgroup | 475/554               | 1.671   | (1.345–2.076) | 0.0   | 3.266     | (1.810–5.891) | 0.0   | 1.482     | (1.127–1.949) | 0.0   | 1.663          | (1.282–2.156) | 0.0   | 2.830          | (1.585–5.052) | 0.0   |

*OR, odds ratio; CI, confidence interval.
Results with statistical significant difference were marked as bold. Unstable results in sensitivity analyses were marked as italic.
FIGURE 2 | Forest plot with a fixed effects model for the association between BAK1 rs210138 and TGCT in allelic comparison (G vs. A) overall. For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. Rhombus: pooled OR and its 95% CI.

FIGURE 3 | Forest plot with an I-V random effects model for the association between BAK1 rs210138 and TGCT in allelic comparison (G vs. A) in total. For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. Rhombus: pooled OR and its 95% CI.
In heterozygote comparison (AG vs. AA), when study NO 1.2 was excluded, statistically different results were obtained (Table 3). No significant publication bias was found in Egger’s test or Begg’s test in either genetic models of overall group. Publication bias was not performed in Caucasian subgroup because of scanty data.

Meta-Analysis in Total
In our eligible GWAS and follow-up studies, we could not retrieve elaborate genotype data. Without elaborate genotype data, sensitivity analyses and potential publication bias were not performed. We tried to perform a meta-analysis based on OR and 95% CIs by using Stata 12.0 software in allelic comparison (G vs. A) (Figure 3), and I–V random effects model was used to get all data shown in Table 4 except overall group. Significantly increased risk of TGCT was found in all groups in Table 4.

DISCUSSION
Above all, we found BAK1 rs210138 guanine (G) was associated with increased risk of TGCT in most genetic models in the meta-analysis of single case-control studies. In GWAS studies, follow-up studies and their meta-analysis based on OR and 95% CIs, BAK1 rs210138 guanine (G) also showed association with increased risk of TGCT in allelic comparison, which was consistent with the results in the meta-analysis of single case-control studies.

Meanwhile, our meta-analysis had several limitations which should be mentioned. Up to now, number of eligible studies for our meta-analysis were small. There was inadequate data for subgroup analyses. Omission of studies in other languages or unpublished studies might happened. In our eligible GWAS and follow-up studies, we could not retrieve elaborate genotype data. With those limitations, the study provided some insights on the potential association between BAK1 rs210138 and TGCT susceptibility.

CONCLUSION
Our results suggested that: Compared with adenine (A), BAK1 rs210138 guanine (G) is associated with increased risk of TGCT. Well-planned studies with larger sample size and more subgroups are needed to verify the risk identified in our systematic review and meta-analysis.

ETHICS STATEMENT
The Ethics Committee of the First Affiliated Hospital of Xiamen University approved the study protocol. Written informed consent was obtained from all patients enrolled in the investigation.

AUTHOR CONTRIBUTIONS
JQ and JX designed the study, drafted and substantively revised the manuscript, and proof the English language. JQ, YY, and XZ accumulated the data. JQ and YY were for analysis and interpretation of the data. All authors read and approved the final manuscript.

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Recently, we (JQ and JX) have published another meta-analysis paper titled Association between CD40 rs1883832 and immune-related diseases susceptibility: A meta-analysis (4). The published paper has no relationship with this manuscript. The published paper and this manuscript used the same statistical method called meta-analysis to study two totally different scientific questions. Owing to the strict report specification (we used PRISMA in both study) of meta-analysis and the first author’s writing habits (JQ), similarity could be found in several sections between the published paper and this manuscript, which needs to be acknowledged here.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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