Association of gene polymorphisms of *KLK3* and prostate cancer: A meta-analysis

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**Abstract**

Previous studies have suggested that prostate-specific antigen (PSA) plays a role in the etiology of prostate cancer (PCa), and that polymorphisms of *KLK3* may be associated with PCa. However, these results were conflicting. Therefore, we performed a meta-analysis to illuminate this problem. We searched the PubMed and Web of Science databases. Ten single nucleotide polymorphisms (SNPs) were involved in this meta-analysis. The pooled results showed that the minor alleles of rs1058205, rs2735839, rs174776, rs17632542, rs266849, rs266878, and rs2569735 were significantly associated with PCa. Compared to genotypes of the common homozygotes, the heterozygous genotypes of rs1058205, rs2735839, rs174776, rs17632542, rs266849, and rs266878 were significantly associated with PCa, as well as the homozygous genotypes of rs1058205, rs2735839, rs17632542, rs266878, and rs2569735. Only rs2735839 was involved in the Gleason score (GS). The pooled results showed that when compared with GS ≥ 8 PCa, the A-allele was the protective factor for GS < 7 PCa. It was also a protective factor for GS ≥ 4+3 when compared to GS ≤ 3+4 PCa. A strong association was observed between PCa and rs1058205, rs2735839, rs266849, rs266878, rs266876, and rs2569735. The G-allele of rs2735839 was a risk factor for GS < 7 PCa when compared with the GS ≥ 8 PCa, as well as for the GS ≥ 4+3 when compared to the GS ≤ 3+4 PCa. Therefore, these SNPs may be valuable as biomarkers for PCa in the future.

**Key words:** *KLK3*, prostate-specific antigen, polymorphisms, prostate cancer, meta-analysis
Prostate cancer (PCa) is the 2nd most frequently diagnosed cancer in men around the world, and one of the leading causes of cancer death among men of all races. With the aging of the population and the improvement of living conditions in recent years, the incidence of PCa has been increasing every year. Serum levels of prostate-specific antigen (PSA) are widely used for screening for PCa. The PSA levels are known to be influenced by genetic components: Around 40–45% of the variance in PSA is thought to be explained by genetic components. Previous studies have revealed that kallikrein 3 (KLK3) is the strongest genetic factor to influence levels of PSA, and its single nucleotide polymorphism (SNP) loci have been shown to be associated with PCa.

The KLK3 is located on chromosome 19q13.33, which encodes PSA and is a member of the serine protease kallikrein family. We searched the PubMed and Web of Science databases without language restrictions up to January 8, 2018, for relevant studies about the association of the SNPs of KLK3 and PCa. We found that nearly 59 SNP loci were mentioned in studies in these databases, and among them, 21 SNP loci were involved in more than 2 studies (Fig. 1). However, these results were conflicting and there was still a lack of any relevant comprehensive analysis to clarify the confusion.

Therefore, in this study, we performed a literature review and a meta-analysis to explore the association between the risk of PCa and the 21 SNP loci of KLK3 that were mentioned in more than 2 studies.

Material and methods

Search strategy

We searched the PubMed and Web of Science databases through September, 2018, without language restrictions, for relevant studies about associations of the SNPs of KLK3 and PCa. The search term was (((KLK3) AND ((single nucleotide polymorphism) OR SNP))) AND ((prostate cancer) OR PSA).

Inclusion/exclusion criteria

The title, abstract and full text of the candidate studies were independently screened by 2 reviewers. A study was included when all of the following criteria were met: 1) Non-familial studies that examined the association between SNPs of KLK3 and PCa were included; 2) studies that had complete data or data that could be used to calculate an odds ratio (OR) and a 95% confidence interval (95% CI) were included; 3) studies that had incomplete data were excluded.

Data extraction

Information was carefully extracted from all the eligible publications by 2 independent reviewers (Li and Fei), based on the aforementioned inclusion criteria. Any disagreements were arbitrated by discussion with a 3rd reviewer (Shen). The following data were collected from each study: the 1st author’s surname, the year of publication, the country, the laboratory methods used to detect KLK3 polymorphisms, and the number of cases and controls.

Quality assessment

We used the Newcastle-Ottawa scale (NOS) to assess the quality of each eligible study. The NOS contains 8 items: 1) The cases were independently validated; 2) Cases were representative of a population; 3) There were community controls; 4) The controls had no history of PCa; 5A) The study was controlled for age; 5B) The study was controlled for additional factors; 6) Exposure was ascertained by blinded interview or record; 7) The same method of ascertainment was used for both the cases and the controls; 8) The non-response rate was the same for the cases and the controls. When a study fulfilled 1 criterion, it got 1 score. The NOS is arranged from 0 up to 9 scores, and a study is considered high quality if it gets more than 4 scores.

Statistical analysis

The strength of the association between KLK3 polymorphism and the risk of PCa was shown using an OR with a 95% CI. If a study just provided the frequency (assumption: the frequency of allele 1 or genotype 1 in the case group was A; the frequency of allele 2 or genotype 2 in the case group was B; the frequency of allele 1 or genotype 1 in the control group was C; the frequency of allele 2 or genotype 2 in the control group was D), we used the formulas “OR = (A/B)/(C/D)” and “95% CI of In OR = In (OR)±1.96(1/ A+1+B+1+C+1/D)0.5” to calculate the OR and its 95% CI.

The statistical significance of the pooled OR was assessed with a Z-test, and a p-value of 0.05 was considered significant. A $\chi^2$-based Q-test was conducted to measure the heterogeneity of the eligible studies, and the heterogeneity was considered significant if the p-value for the heterogeneity test was 0.05. A sensitivity analysis in which 1 study was excluded at a time was conducted to evaluate the influence of an individual study on the results. Beggs’ funnel plot and Egger’s regression test were used to evaluate the publication bias (no publication bias was indicated by a two-sided p-value ≥0.05). All the analyses were conducted using Stata v. 11.0 software (StataCorp LLC, College Station, USA), and a two-sided p-value ≥0.05 indicated no significance.

Results

Literature search

The study selection process is shown in Fig. 2. The primary literature search identified 45 studies. After the titles and abstracts were screened, 13 studies were excluded:
Fig. 1. 59 SNP loci of KLK3 that were mentioned in studies in the databases
3 were reviews and 10 were irrelevant studies. The full texts of the remaining 32 studies were then evaluated. As a result, 12 studies were excluded because of useless data and 21 studies were included in the meta-analysis. The 21 eligible studies were assessed with the NOS (Table 1). Each had a score more than 4, which means that all the studies were of high quality.

**Meta-analysis of associations between SNPs and PCa risk**

We found that 10 SNP loci were available to perform a meta-analysis to illuminate associations between the SNPs of KLK3 and PCa risk. They were rs1058205, rs2735839, rs266882, rs174776, rs17632542, rs266849, rs266878, rs266876, rs1058274, and rs2569735. Their genetic information is presented in Table 2. The pooled results are shown in Table 3.

For the alleles, we found that except rs266882, rs266876 and rs1058274, the remaining 7 SNP loci were significantly

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**Table 1. Characteristics and quality assessment of eligible studies in the meta-analysis**

| Fist author | Patients | Detection method | Year | Quality indicators from NOS | Score |
|-------------|----------|------------------|------|-----------------------------|-------|
| Choe EK⁹    | Korean   | genotyping arrays| 2017 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Chen C⁹     | Chinese  | PCR-HRM          | 2017 | yes  yes  no  yes  yes  yes  yes  yes  yes  yes | 8     |
| Stegeman S¹⁰| European | Illumina Infinium Array | 2015 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| He Y¹¹      | Caucasian men | Illumina BeadXpress Reader | 2014 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Hu J¹²      | Chinese  | TaqMan/MGB Assay | 2014 | yes  yes  yes  no  no  yes  yes  yes  yes  yes | 7     |
| Shui IM¹³   | European | TaqMan Assay     | 2014 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Wang NN¹⁴   | Chinese  | PCR-HRM          | 2013 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Soni A¹⁵    | India    | PCR-RFLP         | 2012 | yes  yes  no  yes  no  yes  yes  yes  yes  yes | 6     |
| Kwon EM¹⁶   | Caucasian and African American men | genotyping arrays | 2012 | yes  yes  yes  yes  no  no  yes  yes  yes  yes | 8     |
| Kote-Jarai Z¹⁷ | UK/Australian | genotyping arrays | 2011 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Penney KL¹⁸ | American | Sequenom technology | 2011 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Lindstrom S¹⁹ | European | TaqMan Assay | 2011 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Ciampa J²⁰  | European | Illumina Chips   | 2011 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Parikh H²¹  | European | TaqMan Assays    | 2011 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Gudmunsson J²² | Icelandic | Illumina Chips | 2010 | yes  yes  no  yes  yes  yes  yes  yes  yes  yes | 7     |
| Gallagher D²³ | Ashkenazi Jewish ancestry | Mass ARRAY QGE iPLEX System | 2010 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Kader AK²⁴  | European | Mass ARRAY QGE iPLEX System | 2009 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Xu J²⁵      | European | Mass ARRAY QGE iPLEX System | 2008 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Eeles RA²⁶  | UK and Australia | sequencing | 2008 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Lai J²⁷     | Caucasian men | PCR-RFLP | 2007 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |
| Ciccek MS²⁸ | American | PCR-RFLP        | 2005 | yes  yes  no  yes  no  no  yes  yes  yes  yes | 6     |

PCR-HRM – high-resolution melting curve polymerase chain reaction method; PCR-RFLP – PCR-restriction fragment length polymorphism; NOS – Newcastle–Ottawa scale.
Table 2. Genetic information for 10 SNPs of KKL3

| SNP          | Chromosome* | Functional consequence* | Position (bp)* | Minor allele | Major allele |
|--------------|-------------|-------------------------|----------------|--------------|--------------|
| rs1058205    | 19:50860142 | URT variant 3 prime     | GRCh38.p7      | T allele     |
| rs2735839    | 19:50861367 | downstream              | GRCh37.p13     | A allele     |
| rs266882     | 19:50854757 | upstream variant 2KB    |                 | A allele     |
| rs174776     | 19:50856596 | intron variant          |                 | T allele     |
| rs17632542   | 19:50858501 | missense                |                 | C allele     |
| rs266878     | 19:50858558 | intron variant          |                 | G allele     |
| rs266876     | 19:50875762 | intron variant          |                 | C allele     |
| rs1058274    | 19:50860192 | URT variant 3 prime     |                 | A allele     |
| rs2569735    | 19:50860103 | downstream variant 500B |                | A allele     |

*The information was provided by the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/); URT – untranslated regions; SNP – single nucleotide polymorphism; KKL3 – kallikrein 3.

Table 3. Meta-analysis of associations between SNPs and PCA risk

| SNP          | Number of studies | Test for overall effect | Test for heterogeneity | Test for publish bias |
|--------------|------------------|-------------------------|------------------------|-----------------------|
|              |                  | OR (95% CI)             | Z-score                | p-value               | i²         | p-value | P_{upper} | P_{lower} |
| rs1058205    |                  |                         |                        |                       |            |         |           |           |
| C allele vs T allele | 8 [9, 10, 16–18, 21] a7 [9, 10, 16–18, 21] | 0.79 (0.73–0.87) | 5.09 | <0.001 | 83.2% | <0.001 | 0.347 | 0.085 | 0.133 |
| TC vs TT     |                  |                         |                        |                       |            |         |           |           |
|              |                  |                         |                        |                       |            |         |           |           |
| CC vs TT     |                  |                         |                        |                       |            |         |           |           |
| rs2735839    |                  |                         |                        |                       |            |         |           |           |
| A allele vs G allele | 14 [8, 12, 14, 17, 19–22, 25, 26] b11 [8, 14, 17, 19–22, 25, 26] | 0.78 (0.71–0.86) | 4.96 | <0.001 | 87.5% | <0.001 | 0.108 | 0.152 | 0.533 |
| AG vs GG     |                  |                         |                        |                       |            |         |           |           |
| AA vs GG     |                  |                         |                        |                       |            |         |           |           |
| rs266882     |                  |                         |                        |                       |            |         |           |           |
| A allele vs G allele | 4 [15, 18, 27, 28] c2 [18, 28] | 1.26 (0.97–1.64) | 1.71 | 0.087 | 83.7% | <0.001 | 0.978 | 0.340 |
| AG vs GG     |                  |                         |                        |                       |            |         |           |           |
| AA vs GG     |                  |                         |                        |                       |            |         |           |           |
| rs174776     |                  |                         |                        |                       |            |         |           |           |
| T allele vs C allele | 3 [16, 18, 21] | 0.86 (0.80–0.93) | 3.74 | <0.001 | 0.0%  | 0.619  | 0.326  | 1.000 |
| CT vs CC     |                  |                         |                        |                       |            |         |           |           |
| TT vs CC     |                  |                         |                        |                       |            |         |           |           |
| rs17632542   |                  |                         |                        |                       |            |         |           |           |
| T allele vs C allele | 4 [17, 22] a3 [17, 22] | 0.61 (0.43–0.86) | 2.79 | <0.001 | 95.0% | <0.001 | 0.134 | 0.659 | 1.000 |
| TC vs CC     |                  |                         |                        |                       |            |         |           |           |
| TT vs CC     |                  |                         |                        |                       |            |         |           |           |
Table 3. Meta-analysis of associations between SNPs and PCa risk – cont.

| SNP | Number of studies | Test for overall effect | Test for heterogeneity | Test for publish bias |
|-----|-------------------|------------------------|-----------------------|----------------------|
|     |                   | OR (95% CI) | Z-score | p-value | I² | p-value | P_{upper} | P_{lower} |
| rs266849 |               |             |        |         |   |         |           |           |
| G allele vs A allele | 8 [17, 19, 26] | 0.81 (0.71–0.92) | 3.16 | 0.002 | 92.2% | <0.001 | 0.036 | 0.289 | 0.462 |
| rs266878 |               |             |        |         |   |         |           |           |
| G allele vs C allele | 2 [18, 21] | 0.86 (0.78–0.94) | 3.23 | 0.001 | 0.0% | 0.410 |           |           |
| ssrs266876 |               |             |        |         |   |         |           |           |
| C allele vs T allele | 2 [18, 21] | 0.83 (0.63–1.08) | 1.42 | 0.157 | 90.9% | 0.001 |           |           |
| rs1058274 |               |             |        |         |   |         |           |           |
| G allele vs A allele | 2 [18, 21] | 0.98 (0.92–1.05) | 0.56 | 0.578 | 0.0% | 0.669 |           |           |
| rs2569735 |               |             |        |         |   |         |           |           |
| A allele vs G allele | 2 [18, 21] | 0.90 (0.82–0.99) | 2.14 | 0.032 | 8.4% | 0.296 |           |           |
| rs266849 |               |             |        |         |   |         |           |           |
| rs266878 |               |             |        |         |   |         |           |           |

associated with the risk of PCa (rs1058205 C vs T allele: OR = 0.79, 95% CI = 0.73–0.87, p-value <0.001; rs2735839 A vs G allele: OR = 0.78, 95% CI = 0.71–0.86, p-value <0.001; rs174776 T vs C allele: OR = 0.86, 95% CI = 0.80–0.93, p-value <0.001; rs17632542 T vs C allele: OR = 0.61, 95% CI = 0.43–0.86, p-value = 0.005; rs266849 G vs A allele: OR = 0.81, 95% CI = 0.71–0.92, p-value = 0.002; rs266878 G vs C allele: OR = 0.86, 95% CI = 0.78–0.94, p-value = 0.001; rs2569735 A vs G: OR = 0.90, 95% CI = 0.82–0.99, p-value = 0.032). For the genotypes, the pooled results showed that the genotype TC (TC vs TT: OR = 0.79, 95% CI = 0.72–0.86, p-value <0.001) and CC (CC vs TT: OR = 0.62, 95% CI = 0.49–0.77, p-value <0.001) of rs1058205, the genotype AG (AG vs GG: OR = 0.80, 95% CI = 0.71–0.91, p-value = 0.001) of rs2735839, the genotype CT (CT vs CC: OR = 0.87, 95% CI = 0.79–0.97, p-value = 0.010) of rs174776, the genotype TC (TC vs CC: OR = 0.57, 95% CI = 0.37–0.87, p-value = 0.009) and TT (TT vs CC: OR = 0.32, 95% CI = 0.14–0.75, p-value = 0.009) of rs17632542, the genotype GA (GA vs AA: OR = 0.80, 95% CI = 0.70–0.91, p-value = 0.001) and GG (GG vs AA: OR = 0.73, 95% CI = 0.55–0.97, p-value = 0.032) of rs266849, the genotype GC (GC vs CC: OR = 0.87, 95% CI = 0.78–0.97, p-value = 0.009) and GG (GG vs CC: OR = 0.72, 95% CI = 0.52–0.98, p-value = 0.036) of rs266878, the genotype CC (CC vs TT: OR = 0.77, 95% CI = 0.65–0.91, p-value = 0.003) of rs266878, and the genotype AA (AA vs GG: OR = 0.72, 95% CI = 0.52–0.99, p-value = 0.042) of rs2569735 were statistically associated with PCa risk, while there was no significance for the genotype AA of rs2735839, the genotype AG and AA of rs266882, the genotype TT of rs174776, the genotype CT of rs266876, the genotype GA and GG of rs1058274, or the genotype AG of rs2569735.

Meta-analysis of associations between SNPs of KLK3 and the Gleason score of PCa

Only rs2735839 was involved in the meta-analysis of associations between SNPs of KLK3 and the Gleason score
As shown in Table 4, when compared with the group of GS ≥ 8 carrier, the A allele was a protective factor for the group of GS < 7 (A vs G allele: OR = 0.598, 95% CI = 0.465–0.770, p-value <0.001); when compared with the group of GS ≤ 3+4 carrier, the G allele was a risk factor for the group of GS ≥ 4+3 (G vs A allele: OR = 1.413, 95% CI = 1.257–1.588, p-value <0.001). When compared with the controls, the G allele was a protective factor for the group of GS < 8 (G vs A allele: OR = 0.841, 95% CI = 0.796–0.889, p-value <0.001), while not significantly associated with the group of GS ≥ 8 (G vs A allele: OR = 1.09, 95% CI = 0.991–1.201, p-value <0.077).

### Meta-analysis for associations between SNPs of KLK3 and fatal PCa risk

SNP rs2735839 was also involved in the meta-analysis of associations between SNPs and the risk of fatal PCa. The pooled result showed that there was no significance between rs2735839 and fatal PCa (G vs A allele: OR = 1.230, 95% CI = 0.725–2.088, p-value = 0.442).

### Heterogeneity test and sensitivity analysis

A heterogeneity test was performed and the results showed that heterogeneity existed in the meta-analysis of associations between the risk of PCa and rs1058205, rs2735839, rs266882, rs17632542, and rs266849. Therefore, a sensitivity analysis was conducted employing the sequential omission of individual studies to find the source of the heterogeneity. As shown in Table 3, after excluding some studies, the heterogeneity was eliminated. Most pooled results were not materially altered, indicating the robustness of the results of this meta-analysis, except the meta-analysis of the genotype (AA vs GG) of rs2735839 and the genotype (GG vs AA) of rs266849. After eliminating the heterogeneity, the genotype AA of rs2735839 was significantly associated with PCa risk (AA vs GG: OR = 0.81, 95% CI = 0.67–0.97, p-value = 0.020), while there was no significant association between the genotype GG of rs266849 and PCa risk (GG vs AA: OR = 0.98, 95% CI = 0.86–1.10, p-value = 0.699).

### Publication bias assessment

Begg’s funnel plot and Egger’s test were performed to assess publication bias in the literature if the number of included studies was more than 3. The results of this meta-analysis showed that no evidence of publication bias was found for any of the analyses.

### Discussion

The etiology and pathogenesis of PCa is still elusive. However, recently, increasing evidence suggests that genetic factors are associated with PCa susceptibility. For many years, PSA, which plays an important role in sperm motility, has been used as a biomarker for PCa screening. The PSA is also involved in the proteolytic breakdown of the extracellular matrix in PCa tumorigenesis, which contributes to tumor invasion and metastasis; high serum PSA correlates with mutations in p53 and overexpression of the B-cell lymphoma 2 protein, which inhibits apoptosis in tumor cells. These findings strongly suggest that PSA plays a role in the etiology of PCa. The PSA protein is encoded by KLK3, and increasing numbers of studies have recently reported that the polymorphisms of KLK3 associated with PSA levels may be associated with PCa. However, these results were conflicting and there was still no comprehensive analysis to clear up the confusion. Therefore, in this study, we performed a literature review and conducted a meta-analysis to explore the association between the SNPs of KLK3 that were analyzed in more than 2 studies and the risk of PCa.

In total, 59 SNPs were mentioned in the literature, and among them, 21 SNPs were involved in more than

| SNP | Number of studies | Test for overall effect | Test for heterogeneity | Test for publish bias |
|-----|-------------------|-------------------------|------------------------|----------------------|
|     |                   | OR (95% CI)            | Z-score                | p-value              | I²         | p-value | P<egger's | P<egger's |
|     |                   |                         |                        |                      |            |          |           |           |
| A allele vs G allele | 3 [12, 24] | 0.598 (0.465–0.770) | 3.99                  | <0.001               | 0.0%       | 0.806    | –         | –         |
| AG/GG vs AA           | 2 [11,12]  | 2.731 (0.622–12.00)   | 1.33                  | 0.183                | 75.5%      | 0.043    | –         | –         |
| G allele vs A allele  | 2 [19, 21] | 0.841 (0.796–0.889)   | 6.14                  | <0.001               | 0.0%       | 0.883    | –         | –         |
| G allele vs A allele  | 2 [19, 21] | 1.09 (0.991–1.201)    | 1.77                  | 0.077                | 0.0%       | 0.517    | –         | –         |
| G allele vs A allele  | 2 [11, 24] | 1.413 (1.257–1.588)   | 5.80                  | <0.001               | 0.0%       | 0.360    | –         | –         |

SNP – single nucleotide polymorphism; GS – Gleason score; PCa – prostate cancer; 95% CI – 95% confidence interval.
2 studies. Finally, 10 SNPs – rs1058205, rs2735839, rs266882, rs174776, rs17632542, rs266849, rs266878, rs266876, rs1058274, and rs2569735 – were eligible to be included in this meta-analysis. The pooled results indicated that the minor alleles of rs1058205 (C allele), rs2735839 (A allele), rs174776 (T allele), rs17632542 (T allele), rs266849 (G allele), rs266878 (G allele), and rs2569735 (A allele) were significantly associated with PCa risk. For the genotype analysis, when compared to genotypes of the common homozygotes (rs1058205: TT, rs2735839: GG, rs174776: CC, rs17632542: CC, rs266849: AA, rs266878: CC, rs266876: TT, and rs2569735: GG), the heterozygote genotype carriers of rs1058205 (CT), rs2735839 (AG), rs174776 (CT), rs17632542 (TC), rs266849 (GA), and rs266878 (GC) had a lower risk of PCa, as did the homozygote genotype carrier of rs1058205 (CC), rs2735839 (AA), rs17632542 (TT), rs266878 (GG), rs266876 (CC), and rs2569735 (AA).

The Gleason grading system remains the most powerful prognostic predictor for PCa because it delineates the architectural patterns of tumors. It is the core value in risk assessment, which incorporates the GS, clinical stage and PSA level of the tumor. Therefore, these SNPs may be valuable as biomarkers for PCa risk. Besides, G allele of rs2735839 was noted as a risk factor for the GS < 7 PCa carrier when compared with GS ≥ 8 PCa, as well as for the GS ≥ 4+3 carrier when compared to the GS ≤ 3+4 PCa carrier. Considering that the quality and quantity of the reviewed articles were limited, larger well-designed studies should be conducted in the future to further confirm the association between KLK3 genetic polymorphisms and PCa.

Conclusions

A strong association was observed between rs1058205, rs2735839, rs266882, rs174776, rs17632542, rs266849, rs266878, rs266876, rs1058274 and rs2569735, and PCa. Therefore, these SNPs may be valuable as biomarkers for PCa risk. Besides, G allele of rs2735839 was noted as a risk factor for the GS < 7 PCa carrier when compared with GS ≥ 8 PCa, as well as for the GS ≥ 4+3 carrier when compared to the GS ≤ 3+4 PCa carrier. Considering that the quality and quantity of the reviewed articles were limited, larger well-designed studies should be conducted in the future to further confirm the association between KLK3 genetic polymorphisms and PCa.

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