Genetic Polymorphisms and Platinum-based Chemotherapy Treatment Outcomes in Patients with Non-Small Cell Lung Cancer: A Genetic Epidemiology Study Based Meta-analysis

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Data regarding genetic polymorphisms and platinum-based chemotherapy (PBC) treatment outcomes in patients with NSCLC are published at a growing pace, but the results are inconsistent. This meta-analysis integrated eligible candidate genes to better evaluate the pharmacogenetics of PBC in NSCLC patients. Relevant studies were retrieved from PubMed, Chinese National Knowledge Infrastructure and WANFANG databases. A total of 111 articles comprising 18,196 subjects were included for this study. The associations of genetic polymorphisms with treatment outcomes of PBC including overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) were determined by analyzing the relative risk (RR), hazard ration (HR), corresponding 95% confidence interval (CI). Eleven polymorphisms in 9 genes, including ERCC1 rs11615 (OS), rs3212986 (ORR), XPA rs1800975 (ORR), XPD rs1052555 (OS, PFS), rs13181 (OS, PFS), XPG rs2296147 (OS), XRCC1 rs1799782 (ORR), XRCC3 rs861539 (ORR), GSTP1 rs1695 (ORR), MTHFR rs1801133 (ORR) and MDR1 rs1045642 (ORR), were found significantly associated with PBC treatment outcomes. These variants were mainly involved in DNA repair (EXCC1, XPA, XPD, XPG, XRCC1 and XRCC3), drug influx and efflux (MDR1), metabolism and detoxification (GSTP1) and DNA synthesis (MTHFR), and might be considered as potential prognostic biomarkers for assessing objective response and progression risk in NSCLC patients receiving platinum-based regimens.

Lung cancer is a leading cause of cancer-associated death and substantially contributes to the heavy burden worldwide, with a dismal 5-year survival rate of 16.6%¹. Among all primary lung cancers, non-small cell lung cancer (NSCLC) represents approximately 85% of cases. Chemotherapy remains the standard first-line treatment for almost 80% of NSCLC patients, of which platinum-based chemotherapy (PBC) is considered as the most efficacious option, especially for patients with an advanced stage of the disease²³. Unfortunately, PBC efficacy varies markedly across individuals. Besides clinical and pathologic features, genetic variation is considered as an important factor to influence the treatment efficacy and prognosis.

For decades, we have witnessed a growing interest in the pharmacogenomics field, and a tremendous amount of epidemiological evidence that gene polymorphisms could give rise to varying drug response has emerged. Many studies have reported the association of genetic factors, including genes related to DNA repair pathway, drug influx and efflux, drug metabolism and detoxification, DNA synthesis, cell cycle control and apoptosis,
with PBC response and prognosis of patients\textsuperscript{4–9}. The accumulation of pharmacogenomics findings calls for a more comprehensive systematic review and meta-analysis to summarize the evidence and to identify the general genetic associations among reported results. Some meta-analyses have studied the influences of certain genes on treatment outcomes of NSCLC patients receiving PBC. However, these findings including original studies are not always consistent, and no systematic review and meta-analysis covering all tested polymorphisms has been performed thus far.

The aim of this work is to identify the effects of all eligible genes in clinical prognosis of NSCLC patients receiving platinum-based treatment. A total of 24 single nucleotide polymorphisms (SNPs) of 12 genes (\textit{ERCC1}, \textit{XPA}, \textit{XPC}, \textit{XPD}, \textit{XRCC1}, \textit{XRCC3}, \textit{GSTP1}, \textit{MTHFR}, \textit{RRM1}, \textit{MDR1} and \textit{CDA}) have been studied in our work. The impacts of these genetic variants on PBC efficacy in NSCLC patients were assessed by evaluating the objective response ratio (ORR), progression-free survival (PFS), and overall survival (OS). We think this comprehensive meta-analysis with robust evidence would fill the gap in the pharmacogenomics of platinum in NSCLC patients.

Materials and Methods

Search strategy, eligibility criteria and data extraction. We followed the principles proposed by the Human Genome Epidemiology Network (HuGeNet) HuGe Review Handbook of Genetic Association Studies\textsuperscript{9}.

Relevant studies were searched in PubMed, Chinese National Knowledge Infrastructure (CNKI) and WANFANG databases. A two-step search strategy was implemented and last updated on January 31, 2016. First, the following three groups of keywords were used for searching in MEDLINE (via the PubMed gateway): platinum OR cisplatin OR carboplatin OR oxaliplatin OR nedaplatin, polymorphism OR SNP OR variant, NSCLC OR non-small cell lung cancer. Second, we used different combinations of the above terms for complementary searching. Besides, references cited in the retrieved papers were manually searched in case of missing relevant studies. Afterwards, we singled out the candidate genes that were eligible in our research, and the terms including a candidate gene's official symbol and the three above-mentioned groups of keywords were used to perform a comprehensive search.

The studies included in the meta-analysis had to meet all the following inclusion criteria: (i) cancer should be confirmed as NSCLC; (ii) treatment regimens were platinum-based chemotherapies; (iii) studies provided primary outcomes of interest including ORR, PFS or OS. Studies met any one of the exclusion criteria listed below were excluded in our analysis: (i) studies without indispensable data such as genotypes, overall response rate (ORR), overall survival (OS), or progression-free survival (PFS); (ii) studies with other types of lung cancer such as small cell lung cancer (SCLC) included; (iii) reviews, case reports, and meta-analyses. (iv) studies based on cell lines and animal experiment.

All records were screened by three investigators independently (Tan, Qiu and Jin) with disagreement resolved by discussion. The following information was extracted from each of the eligible studies: first author, publication year, sample size, ethnicity, age, gender, stages of tumor, chemotherapeutic agents, SNPs and genotyping methods, treatment outcomes.

Statistical analysis. We used the ORR as an indicator for PBC efficacy. Patients were classified into two groups: the responding group, which included complete and partial responders (CR and PR), and the non-responding group, which included subjects with stable or progressive diseases (SD and PD)\textsuperscript{10}. RR and the corresponding 95% CI were used to assess the association between each genetic variant and the response of NSCLC patients treated with PBC. The hazard ratios (HR) and corresponding 95% CI were determined to evaluate OS and PFS. Three genotypic models commonly used in genetic association synopses were applied in this meta-analysis: heterozygous or homozygous variant versus wild type, heterozygous variant versus wild type and homozygous variant versus wild type.

Between-study variance, also known as heterogeneity, was evaluated by the chi-square-based \textit{Q} test based on chi-square as well as \textit{I}^2. \textit{Q} tests with \textit{P} > 0.10 were considered with statistical significance. \textit{I}^2 described the proportion of variation originating from heterogeneity rather than within-study error, whose value varied from 0 to 100 percent and indicated different heterogeneity degrees. Heterogeneity could be accepted when \textit{I}^2 < 50\% (0 < \textit{I}^2 < 25\%: no heterogeneity; 25 \textit{I}^2 < 50\%: moderate heterogeneity). Sensitivity analysis and subgroup analysis were also applied to find the source of heterogeneity. Pooled RRs and HRs were calculated using the fixed-effects model when the heterogeneity was under the moderate degree or did not exist. Otherwise, the random-effects model was used. Moreover, the potential publication bias was assessed by statistical evaluation with Begg’s funnel plot and Egger’s linear regression test. The \( \alpha \) level of significance was set at 0.05 unless noted otherwise.

In the end, we calculated the false positive report probability (FPRP) of statistically significant results to assess whether the findings were noteworthy\textsuperscript{11}. The FPRP value was determined based on the \( P \) value, the prior probability for the association and statistical power. We set a stringent FPRP threshold of 0.20 and assigned a prior probability range of 0.1–0.001, and the statistical power was based on the ability to detect an OR of 1.5, with \( \alpha \) equal to the observed \( p \)-value.

All statistical analyses were performed with STATA/SE 12.0 (StataCorp, College station, TX) and R (version 3.2.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Eligible Studies. After the process of selection, a total of 111 studies met the inclusion criteria and totally 18,196 NSCLC subjects (between the ages of 51 to 84) who accepted PBC were included in the final meta-analysis. More than 80% of these articles focused on the advanced NSCLC (in disease stages of III–IV).
The process of selecting publications is presented in Fig. 1 and more details about the characteristics of the studies included are listed in Table 1.

**Meta-analysis findings.** Genetic variants associated with response to platinum drugs. As shown in Table 2, we conducted 74 primary meta-analyses and 64 subgroup meta-analyses sorted by ethnicity to study the associations between 24 SNPs of 12 genes and the responses to PBC in NSCLC patients. Of the 138 performed meta-analyses, 26 (19%) resulted in statistically significant ($P < 0.05$), with the remaining 112 being non-significant. For ORR, RR $< 1$ indicated that patients carrying the allele or genotype had a disadvantageous response, RR $> 1$ donated that the allele carriers had a favorable response. Pooled RR with 95% CI of individual SNPs identified as statistically associated with favorable responses to PBC were listed as follows:

- **XRCC1** rs25487 (AA vs. GG: overall RR $= 1.27$, 95% CI $= 1.02–1.58$), **XRCC1** rs1799782 (CT vs. CC: overall RR $= 1.22$, 95% CI $= 1.07–1.56$), **XRCC3** rs861539 (CT VS CC: Caucasian RR $= 1.46$, 95% CI $= 1.06–1.99$ and overall RR $= 1.31$, 95% CI $= 1.07–1.59$; TT VS CC: Caucasian RR $= 1.59$, 95% CI $= 1.07–2.36$ and overall RR $= 1.48$, 95% CI $= 1.12–1.97$; TT+CT VS CC: Caucasian RR $= 1.48$, 95% CI $= 1.10–2.01$ and overall RR $= 1.28$, 95% CI $= 1.07–1.52$), **XPA** rs1800975 (AG VS AA: Asian RR $= 2.17$, 95% CI $= 1.29–3.64$ and overall RR $= 1.74$, 95% CI $= 1.18–2.57$), **GSTP1** rs1695 (GG vs. AA: overall RR $= 0.71$, 95% CI $= 0.54–0.94$ and overall RR $= 0.72$, 95% CI $= 0.56–0.94$), **XRCC1** rs13181 (CA+CC vs. AA: Asian RR $= 0.83$, 95% CI $= 0.71–0.98$), **ERP1** rs1799793 (AA vs. GG: Asian RR $= 0.20$, 95% CI $= 0.05–0.76$), **MTHFR** rs1801133 (CT vs. CC: mixed RR $= 0.63$, 95% CI $= 0.44–0.89$), **MDR1** rs1045642 (CT vs. CC: Asian RR $= 0.69$, 95% CI $= 0.50–0.95$ and overall RR $= 0.73$, 95% CI $= 0.56–0.94$; TT vs. CC: Asian RR $= 0.47$, 95% CI $= 0.26–0.85$ and overall
| First author (Year) | Ethnicity (country) | Sample size | Male/female | Median age | Disease stage | Chemotherapeutic drugs | Outcomes | Genotyping method | SNPs | Ref.  |
|---------------------|--------------------|-------------|-------------|------------|--------------|------------------------|----------|------------------|------|------|
| Camps, C. (2003)    | Caucasian (Spain)  | 39          | 34/5        | 64 (27–82) | IIIB–IV      | DDP+GEM               | OR       | Direct sequencing | XPD rs1799793 rs13181 | 12   |
| Ryu, J. S. (2004)   | Asian (Korea)      | 109         | 88/21       | 60 (32–78) | IIIB–IV      | DDP+TAX/GEM/DOC       | OR       | SNPShot assay    | ERCCI rs11615 XPD rs179973 rs13181 | 13   |
| Gurubhagavatula, S. (2004) | Caucasian (USA) | 103         | 53/50       | 58 (32–77) | IIIA–IV     | DDP/CBP-based         | OS       | PCR-RFLP         | XPD rs179973 XRCXI rs25487 | 14   |
| Isla, D. (2004)     | Caucasian (Spain)  | 62          | 48/14       | 62 (35–78) | IIIB–IV      | DDP+DOC               | OR       | TaqMan         | ERCCI rs11615 rs3212986 | 15   |
| Zhou, W. (2004)     | Caucasian (USA)    | 128         | 66/62       | 60 (32–78) | IIIA–IV     | Platinum based        | OS       | PCR-RFLP        | ERCCI rs1799782 | 16   |
| Wang, Z. H. (2004)  | Asian (China)      | 105         | 59/46       | 56 (30–74) | IIIB–IV      | DDP/CBP+NVB/TAX/DOC   | OR       | PCR-RFLP        | ERCCI rs3212986 XPD rs13181 XPC PAT | 17   |
| Yuan, P. (2005)     | Asian (China)      | 200         | 130/70      | 56 (30–74) | IIIA–IV     | Platinum based        | OR       | PCR-RFLP        | ERCCI rs16615 | 18   |
| Lu, C. (2006)       | Caucasian+Mexican/African American | 425         | 236/198     | NR         | III–IV      | Platinum based        | OS       | PCR-RFLP        | GSTP1 rs1695 | 19   |
| de Las, F. R. (2006) | Caucasians (Spain) | 135        | 125/10      | 62 (31–81) | IIIB–IV      | DDP+GEM               | OS       | TaqMan         | ERCCI rs16615 XPD rs1799793 XRCXI rs25487 | 20   |
| Booton, R. (2006)   | Caucasian (UK)     | 108         | 74/34       | 62.5 (35–80) | III–IV      | DDP/CBP-based         | OR       | PCR-RFLP        | XPD rs13181 rs1799793 | 21   |
| Yuan, P. (2006)     | Asian (China)      | 200         | 130/70      | 56 (30–74) | IIIB–IV      | DDP/CBP+NVB/TAX/DOC   | OR       | PCR-RFLP        | XRCXI rs1799782 | 22   |
| Booton, R. (2006a)  | Caucasian (UK)     | 108         | 74/34       | 62.5 (35–80) | III–IV      | DDP/CBP-based         | OR, OS  | PCR-RFLP        | GSTP1 rs1695 | 23   |
| Shi, M. (2006)      | Asian (China)      | 97          | 67/30       | 60 (22–81) | II–IV       | Platinum based        | OR       | PCR-RFLP        | MTHFR rs1801133 | 24   |
| Shi, M. (2006a)     | Asian (China)      | 112         | 81/31       | 60 (22–81) | II–IV       | Platinum based        | OR       | PCR-RFLP        | XRCXI rs25487 rs1799782 | 25   |
| Su, D. (2007)       | Asian (China)      | 76          | 179/51      | 58 (28–80) | III–IV      | Platinum based        | OR       | TaqMan         | ERCCI rs11615 | 26   |
| Sun, X. C. (2007)   | Asian (China)      | 96          | 62/34       | 58 (34–77) | IV          | DDP/CBP-based         | OR       | PCR-cDNA        | XPA rs1800975 | 27   |
| Song, D. G. (2007)  | Asian (China)      | 166         | 97/69       | 56 (30–68) | III–IV      | DDP+/NVB/DOC/GEM     | OR       | PCR-RFLP        | XPD rs1799793 | 28   |
| Yu, Q. Z. (2007)    | Asian (China)      | 101         | 78/23       | 57 (30–72) | III–IV      | DDP-based             | OR       | PCR-RFLP        | XPG rs17655  MDR1 rs1045642 | 29   |
| Pan, J. H. (2008)   | Asian (China)      | 69          | 48/21       | 55 (30–76) | IIIB–IV     | DDP+NVP               | OR       | PCR-RFLP        | MDR1 rs1045642 | 30   |
| Tibaldi, C. (2008)  | Caucasian (Italy)  | 65          | 51/14       | 65 (44–77) | IIIB–IV     | DDP+GEM               | OR, OS  | TaqMan         | ERCCI rs11615 XPD rs13181 rs1799793 CDA rs2072671 | 31   |
| Wu, X. (2008)       | Caucasian (USA)    | 229         | 135/94      | NR         | III–IV     | Cisplatin-based       | OS       | TaqMan         | ERCCI rs3212986 XPG rs17655 GSTPI rs1695 MDR1 rs1045642 XPA rs1800975 XPC rs2228001 XPC rs2228000 | 32   |
| Din, Z. H. (2008)   | Asian (China)      | 116         | 85/31       | 60 (22–81) | IIIB–IV     | DDP+GEM               | OR       | PCR-RFLP        | XPD rs13181 | 33   |
| Liu, X. Z. (2008)   | Asian (China)      | 53          | 38/15       | 61 (28–74) | I–IV        | DDP/CBP-based         | OS       | TaqMan         | XPD rs13181 | 34   |
| Pan, J. H. (2009)   | Asian (China)      | 54          | 38/16       | 55 (30–76) | IIIB–IV     | DDP+DOC               | OR       | PCR-RFLP        | MDR1 rs1045642 | 35   |
| Sun, X. (2009)      | Asian (China)      | 82          | 53/29       | 59 (34–79) | IV          | DDP/CBP-based         | OR       | 3D DNA        | XPG rs1047768 rs17655 XRCXI rs25487 rs1799782 | 36   |
| Feng, J. F. (2009)  | Asian (China)      | 214         | 158/56      | 59 (21–75) | III–IV      | Platinum-based        | OR       | PCR-RFLP        | RMAI rs12806698 | 37   |
| Feng, J. E. (2009a) | Asian (China)      | 115         | 78/37       | 59.6 (34–84) | III–IV      | DDP/CBP-based         | OR       | DNA microarray   | XPA rs1800975 | 38   |
| Kalikaki, A. (2009) | Caucasian (Greece) | 119         | 101/18      | 61 (39–85) | III–IV      | Platinum-based        | OR, OS  | PCR-RFLP        | ERCCI rs3212986 XPD rs13181 rs1799793 GSTPI rs1695 | 39   |
| Hong, C. Y. (2009)  | Asian (China)      | 164         | 99/65       | 61 (27–84) | IIIB–IV     | DDP+NVP               | OR       | PCR-RFLP        | XRCXI rs25487 rs1799782 | 40   |
| Gao, C. M. (2009)   | Asian (China)      | 57          | 44/13       | 59 (38–77) | II–IV       | DDP+GEM               | OR       | PCR-RFLP        | XRCXI rs1799782 | 41   |

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| First author (Year) | Ethnicity (country) | Sample size | Male/female | Median age | Disease stage | Chemotherapeutic drugs | Outcomes | Genotyping method | SNPs | Ref. |
|---------------------|---------------------|-------------|-------------|------------|--------------|------------------------|---------|------------------|------|------|
| Hu, S N. (2009)     | Asian (China)       | 214         | 158/56      | 59 (22–81) | II–IV        | Platinum based         | OR      | PCR-RFLP          | RRM1 rs12806698 | 42   |
| Takenaka, T. (2010) | Asian (Japan)       | 122         | 75/47       | 69 (30–86) | I–III        | platinum-based         | OS      | Direct sequencing  | rs11615 | 43   |
| Sun, N. (2010)      | Asian (China)       | 113         | 76/37       | 59.6       | IIIA-IV      | DDP/CPB-based          | OR      | 3-D polycrylamide gel-based DNA microarray | GSTP1 rs1695 | 44   |
| Chen, S. (2010)     | Asian (China)       | 95          | 76/19       | 58 (35–77) | IIIB-IV      | Platinum based         | OR      | LDR              | rs11615 | 45   |
| Li, E. (2010)       | Asian (China)       | 115         | 78/37       | 60 (NR)    | IIIB-IV      | Platinum based         | OR      | 3-D polycrylamide gel-based DNA microarray | rs13181 | 46   |
| Zhou, C. (2010)     | Asian (China)       | 130         | 74/56       | 61 (30–78) | IIIA-IV      | Platinum-based         | OR      | TaqMan           | rs11615 | 47   |
| Zhu, X. L. (2010)   | Asian (China)       | 96          | 64/32       | 57 (34–79) | III-IV       | DDP/CPB+/NVB/TAX/GEM   | OR      | DNA microarray genotyping | rs861539  | 48   |
| Wang, J. (2010)     | Asian (China)       | 90          | 63/27       | 55 (33–73) | III-IV       | DDP+/NVB/TAX/GEM/DO/C  | OR      | Direct sequencing  | rs11615 | 49   |
| Yuan, P. (2010)     | Asian (China)       | 199         | 129/70      | 56 (29–74) | IIIA-IV      | Platinum-based         | OS, PFS | PCR-RFLP          | rs25487 | 50   |
| Okuda, K. (2011)    | Asian (Japan)       | 90          | 73/17       | NR         | I-IV         | Platinum-based         | OS      | PCR-RFLP          | rs11615 | 51   |
| Vinolas, N. (2011)  | Caucasian (Spain)   | 94          | 79/15       | 61 (37–77) | IIIA-IV      | DDP+NVP                | OR, OS  | 5′ nuclease allelic discrimination assay | rs25487 | 52   |
| Liu, L. (2011)      | Asian (China)       | 199         | 129/70      | 56 (29–74) | IIIA-IV      | Platinum-based         | OS, PFS | PCR–RFLP          | rs13181 | 53   |
| KimCurran, V. (2011)| Asian (China)       | 300         | 201/99      | 60 (33–78) | IIIB-IV      | DDP/CPB+/NVB/TAX/GEM   | OR      | RT-PCR           | rs3212986 | 54   |
| Cui, L. H. (2011)   | Asian (China)       | 101         | 62/39       | 58 (27–76) | IIIB-IV      | DDP/CPB-based          | OR      | MTHFR rs1801133   | rs11615 | 55   |
| Ryu, J. S. (2011)   | Asian (Korea)       | 298         | 236/62      | 63 (28–89) | IIIB-IV      | DDP+GEM/TAX            | OS      | SBE              | rs861539 | 56   |
| Zhou, F. (2011)     | Asian (China)       | 111         | 67/44       | 57 (42–71) | IV           | DDP+/DO/C/GEM/NVB/PEM  | OR      | Direct sequencing  | rs11615 | 57   |
| Zhai, Y. N. (2011)  | Asian (China)       | 163         | 98/65       | 61 (27–84) | IV           | DDP+NVP                | OR, OS  | PCR-RFLP          | rs25487 | 58   |
| Ludovini, V. (2011) | Caucasian (Italy)   | 192         | 142/50      | 63 (25–81) | IIIB-IV      | DDP-based              | OR      | TaqMan           | rs13181 | 59   |
| Xu, C. (2011)       | Asian (China)       | 130         | 90/40       | NR          | IIIB-IV      | Platinum-based         | OR      | PCR-RFLP          | rs11615 | 60   |
| Yan, P. W. (2011)   | Asian (China)       | 103         | 67/36       | 61 (39–79) | IIIB-IV      | Platinum-based         | OR      | RT-PCR           | rs1045642 | 61   |
| Cheng, H. Y. (2011)| Asian (China)       | 120         | 82/38       | 58 (34–77) | NR           | DDP/CPB-based          | OR      | Two-color fluorescent probe hybridization | rs25487 | 62   |
| Jia, X F. (2011)    | Asian (China)       | 89          | 45/44       | NR          | III-IV       | DDP/CPB+/DO/C/GEM      | OR      | Direct sequencing  | rs1047768 | 63   |
| Li, D. R. (2011)    | Asian (China)       | 89          | 64/25       | 59 (21–84) | IIIA-IV      | DDP-based              | OR      | Direct sequencing  | rs25487 | 64   |
| Li, D. R. (2011a)   | Asian (China)       | 89          | 64/25       | 59 (21–84) | IIIA-IV      | DDP-based              | OR      | Direct sequencing  | rs1799793 | 65   |
| Zhao, W. (2011)     | Asian (China)       | 151         | 92/59       | 62 (32–82) | IIIB-IV      | DDP/CPB-based          | OR      | TaqMan           | rs25487 | 66   |
| Zhou, F. (2011a)    | Asian (China)       | 94          | 55/39       | 57 (42–71) | IIIB-IV      | DDP-based              | OR      | Direct sequencing  | rs13181 | 67   |
| Ren, S. (2012)      | Asian (China)       | 340         | 232/108     | 60 (30–78) | IIIA-IV      | DDP+/NVB/GEM/TAX/DO/C  | OR, OS  | TaqMan           | rs13181 | 68   |
| Dong, J. (2012)     | Asian (China)       | 568         | 434/134     | 60 (25–83) | III–IV       | Platinum-based         | OS      | TaqMan           | rs11615, rs25487 | 69   |
| Li, D. (2012)       | Asian (China)       | 89          | 64/25       | 59 (21–84) | III-IV       | DDP+/NVB/TAX/DDP/GEM/DO | OR      | PCR-RFLP          | rs11615 | 70   |

Continued
| First author (Year) | Ethnicity (country) | Sample size | Male/female | Median age | Disease stage | Chemotherapeutic drugs | Outcomes | Genotyping method | SNPs | Ref. |
|---------------------|--------------------|-------------|-------------|------------|--------------|----------------------|----------|--------------------|------|------|
| Butkiewicz, D. (2012) | Caucasian (Poland) | 171         | NR          | I–IV       | Platinum based OR PCR-RFLP | TaqMan | XPCR rs11615 |     |    |    |
| Dogu, G. G. (2012) | Caucasian (Turkey) | 79          | 72/7        | 60 (32–84) | IB-IV | Platinum based OS | PCR-RFLP | MRDR1 rs1045642 |    |    |
| Ke, H. G. (2012) | Asian (China) | 460         | 334/126     | 55 (32–79) | I-IV | DDP-based OS | PCR-CTPP | XPCR1 rs25487, XRC3C rs8161539 |    | 79 |
| Liu, H. N. (2013) | Asian (China) | 62          | 38/24       | 58 (37–72) | IIIB-IV | DDP+NV/P TAX/ GEM | TaqMan | XPCR1 rs25487, GSTP1 rs1695 |    |    |
| Zhang, Y P. (2012) | Asian (China) | 62          | 38/24       | 58 (37–72) | IIIB-IV | DDP+NV/P TAX/ GEM | TaqMan | GSP1 rs1695 |    |    |
| Krawczyk, P. (2012) | Caucasian (Poland) | 43          | 33/10       | 63 (NA) | IIIB–IV | Platinum based OR | PCR-RFLP | ERCC1 rs11615 |    |    |
| Liao, W. Y. (2012) | Asian (Taiwan) | 62          | 35/27       | 57 (36–78) | III- IV | DDP+GEM | OR, OS, TaqMan | XPCR1 rs11615 |    |    |
| Ke, H. G. (2012) | Asian (China) | 460         | 334/126     | 55 (32–79) | I-IV | DDP-based OS | PCR-CTPP | XPCR1 rs25487, XRC3C rs8161539 |    | 79 |
| Liu, H. N. (2013) | Asian (China) | 62          | 38/24       | 58 (37–72) | NR | DDP-based OR | TaqMan | XPCR1 rs25487 |    |    |
| Zhao, W. (2013) | Asian (China) | 147         | 92/55       | 60 (32–82) | IIIB-IV | Platinum-based OR, OS, PFS | TaqMan | XPCR1 rs25487, XRC3C rs1695 |    |    |
| Li, X. D. (2013) | Asian (China) | 496         | 324/172     | 63 (33–79) | IIIA-IV | Platinum-based OR, OS, PFS | PCR-SBE | XPCR1 rs3181, XPCR1 rs1799793, XRC3C rs1052555 |    |    |
| Li, W. I. (2013) | Asian (China) | 45          | 23/22       | 63 (39–81) | IIIB-IV | DDP+PEM | TaqMan | MT4F3 rs1801133 |    |    |
| Cheng, H. (2013) | Asian (China) | 115         | 78/37       | 59.6 (34–84) | IIIB-IV | Platinum-based OS, PFS 3-D polyacrylamide gel-based DNA | XPCR1 rs3181, XPC rs1800975 |    |    |
| Zhang, T. (2013) | Asian (China) | 475         | 306/145     | 64 (32–76) | III-IV | DDP+DOC, DDP/ CBP+GEM/NV B | OR, PFS, TaqMan | XPCR1 rs25487, XRC3C rs1799792 |    |    |
| Lee, S. Y. (2013) | Asian (Korea) | 382         | 311/71      | NR | III-IV | DDP+TAX | OR, OS, Sequenome mass spectrometry-based | XPCR1 rs1052555, XRC3C rs25487 |    |    |
| Milak, R. (2013) | Caucasian (Poland) | 62          | 43/19       | 61 (38–76) | IIIA-IV | Platinum-based OS | PCR-RFLP | REMI rs12806698 |    |    |
| Yuli, Y. (2013) | Asian (China) | 433         | 284/149     | 61 (33–79) | IIIA-IV | DDP+CBP-based OS, PFS | TaqMan | XPCR1 rs7655 |    |    |
| Lu, H D. (2013) | Asian (China) | 100         | 54/46       | 61 (41–82) | III-IV | DDP+NV/B TAX/ OR | PCR-RFLP | ERCC1 rs11615 |    |    |
| Sheng, F. E. (2013) | Asian (China) | 62          | 38/24       | 58 (37–72) | NR | DDP-based OR | TaqMan | XPCR1 rs25487 |    |    |
| Yang, W J. (2013) | Asian (China) | 54          | 38/16       | 56 (30–73) | III-IV | DDP+CBP-based OR | PCR-RFLP | XPCR1 rs1799792, XRC3C rs1052555 |    |    |
| Zhang, Y P. (2013) | Asian (China) | 62          | 38/24       | 58 (37–72) | NR | DDP+NV/B TAX/ GEM/PEM | OR, OS, TaqMan | XPCR1 rs3181, XPCR1 rs12806698 |    |    |
| Zhou, G R. (2013) | Asian (China) | 204         | 120/84      | 61 (45–75) | NR | DDP-based OR | MALDI-TOF- MS | XPCR1 rs25487 |    |    |
| Huang, S. J. (2014) | Asian (China) | 187         | 124/63      | NR | IIIA-IV | Platinum-based OR, OS, MALDI-TOF- MS | XPCR1 rs11615 |    |    |
| Zhang, L. (2014) | Asian (China) | 375         | 249/126     | NR | IIIA-IV | CBP+NV/PP, DDP+DOC | OR, OS, PFS, Sequenome MassARRAY platform | XPCR1 rs3181, XPCR1 rs1799793, XRC3C rs1052555 |    |    |

Continued
| First author (Year) | Ethnicity (country) | Sample size | Male/female | Median age | Disease stage | Chemotherapeutic drugs | Outcomes | Genotyping method | SNPs | Ref. |
|---------------------|---------------------|-------------|-------------|------------|---------------|-----------------------|----------|------------------|------|------|
| Jin, Z. Y. (2014)   | Asian (China)       | 378         | 297/81      | 62.4       | 1-IV          | DDP+GEM/DOC/ NVP/TAX | OR, OS   | PCR-RFLP         | XPG rs1047768 rs17655, XRCC1 rs25489, XRCC3 rs861539 | 101  |
| Hu, W. (2014)       | Asian (China)       | 277         | 184/93      | 63.1       | IIIA-IV       | Platinum-based       | OS, PFS  | PCR-RFLP         | XPG rs1047768 rs17655 rs2296147 rs873601 | 102  |
| Peng, Y. (2014)     | Asian (China)       | 235         | 180/55      | 58 (29–84) | IIIA-IV       | DDP+TAX/DOC/GEM      | OR, OS   | PCR-CTTP         | XRCC1 rs25487                        | 103  |
| Zhou, M. (2014)     | Asian (China)       | 93          | 56/37       | 61.5       | IIIIB-IV      | DDP+GEM              | OR       | PCR-RFLP         | XPD rs13181 rs1799733, CD4 rs2072671 | 104  |
| Zhao, X. (2014)     | Asian (China)       | 192         | 132/60      | 60.8       | IIIA-IV       | Platinum-based       | OR, OS   | MALDI-TOF-MS     | ERCC1 rs3122986 rs16165 rs2298881    | 105  |
| Lv, H. (2014)       | Asian (China)       | 91          | 54/37       | 59 (34–80) | IIIIB-IV      | DDP+TAX/GEM/NVP     | OR       | TaqMan-MGB       | GSTP1 rs1695                        | 106  |
| Krawczyk, P. (2014) | Caucasian (Poland)  | 115         | 59/56       | 61 (NR)    | II-IV         | DDP/CBP+FEM          | OS       | HRM, PCR-RFLP    | ERCC1 rs16165                      | 107  |
| Sullivan, I. (2014) | Caucasian (Spain)   | 161         | 125/36      | 63.7       | IIIA-IV       | DDP/CBP-based        | OR, OS   | Dynamic array chips | ERCC1 rs3122986 rs16165, XPD rs13181 rs1799733, XPG rs1047768 rs17655, XRCC1 rs25487 rs1799782 rs25489, XPA rs1809075 | 108  |
| Dong, C. M. (2014)  | Asian (China)       | 92          | 38/54       | 57 (40–60) | IIIIB-IV      | Platinum-based       | OR       | PCR-RFLP         | MTHFR rs1801133                   | 109  |
| Liu, D. (2014)      | Asian (China)       | 378         | 297/81      | 62.4       | 1-IV          | DDP+GEM/DOC/ NVP/TAX | OR, OS   | PCR-RFLP         | XPG rs1047768 rs17655, XRCC1 rs25487 rs1799782 | 110  |
| Kou, G. (2014)      | Asian (China)       | 50          | 14/36       | 56 (45–78) | IIIIB-IV      | DDP+NVP              | OR       | PCR-RFLP         | ERCC1 rs3122986 rs16165            | 111  |
| Kalikaki, A. (2015) | Caucasian (Greece)  | 107         | 90/17       | 60 (37–78) | IIIIB-IV      | DDP/CBP-based        | OR, OS   | PCR-RFLP         | ERCC1 rs3122986, XRCC1 rs25487     | 112  |
| Zou, H. Z. (2015)   | Asian (China)       | 246         | 170/76      | 64.3       | IIIA-IV       | DDP/CBP-based        | OR, OS   | PCR-RFLP         | XPG rs2296147 rs873601             | 113  |
| Yuan, Z. J. (2015)  | Asian (China)       | 47          | 42/5        | 59 (29–74) | III-IV        | DDP+GEM              | OR       | DNA sequencing   | GSTP1 rs1695                        | 114  |
| Deng, I. H. (2015)  | Asian (China)       | 97          | 66/31       | 57 (31–79) | IIIIB-IV      | DDP+GEM/NVP/TAX/DOC  | OR, PFS  | DNA pyrosequencing | XRCC1 rs25487, GSTP1 rs1695        | 115  |
| Shi, Z. H. (2015)   | Asian (China)       | 240         | 155/85      | 61.5       | III-IV        | DDP+GEM/NVP/TAX/DOC  | OR, OS   | PCR-RFLP         | ERCC1 rs16165 rs3122986 rs2298881   | 116  |
| Han, B. (2015)      | Asian (China)       | 325         | 116/209     | NR         | IIIB-IV      | DDP+GEM/NVP/TAX/DOC  | OR       | PCR-RFLP         | XRCC1 rs25487 rs1799782 rs25489, GSTP1 rs1695 | 117  |
| Li, P. (2015)       | Asian (China)       | 142         | 89/53       | 62 (43–81) | IIIB-IV      | DDP+NVP              | OR       | PCR-RFLP         | XPD rs13181 rs1799733               | 118  |
| Liu, J. Y. (2015)   | Asian (China)       | 322         | 226/140     | 62.5       | IIIB-IV      | DDP+GEM/NVP/TAX/DOC  | OR, OS   | PCR-RFLP         | XRCC1 rs25487 rs1799782, GSTP1 rs1695 | 119  |
| Wu, G. (2015)       | Asian (China)       | 282         | 181/101     | NR         | IIIA-IV      | DDP-based            | OR, OS   | PCR-RFLP         | GSTP1 rs1695                        | 120  |
| Zhu, M. Z. (2015)   | Asian (China)       | 68          | 40/28       | NR         | IIIIB-IV      | DDP/CBP-based        | OR       | PCR-RFLP         | ERCC1 rs16165                      | 121  |

**Table 1.** The baseline characteristics of the studies included in this meta-analysis. NR, no report; DDP, cisplatin; CBP, carboplatin; GEM, gemcitabine; NVP, vinorelbine; PEM, pemetrexed; TAX, taxol/paclitaxel; DOC, docetaxel; LDR, Ligase detection reactions; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SBE, single base extension; HRM, High Resolution Melt; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time-of flight mass.

RR = 0.52, 95% CI = 0.34–0.81; CT+TT vs. CC. Asian RR = 0.61, 95% CI = 0.48–0.79 and overall RR = 0.64, 95% CI = 0.52–0.80).

**Genetic variants associated with OS and PFS.** Statistically significant results with HR > 1 indicated that patients carrying the allele or genotype harbored a poorer OS or PFS, while with HR < 1 meant better OS or PFS of patients. As for OS (Table 3), 52 meta-analyses were preformed to examine the influence of 22 SNPs in 11 genes on the overall survival. Seven results were identified as statistically significantly associated with OS. Of them, ERCC1 rs16165 (CT+TT vs. CC; HR = 1.47, 95% CI = 1.15–1.88), ERCC1 rs3212986 (AA vs. CC; HR = 2.06, 95% CI = 1.39–3.57), XPD rs13181 (AA+CC vs. AA; HR = 1.24, 95% CI = 1.07–1.44), and XPD rs1052555 (CT+TT vs. CC; HR = 1.71, 95% CI = 1.31–2.23) might be related to a poorer OS, while XPG rs873601 (GG vs. AA; HR = 0.67, 95% CI = 0.46–0.97), XPG rs2296147 (TT vs. CC; HR = 0.40, 95% CI = 0.27–0.61), and XPD
rs1799793 (GA vs. GG: HR = 0.78, 95% CI = 0.62–0.99) might be potentially related to a better OS. No significant association was identified in the remaining SNPs. As for PFS (Table 4), 19 meta-analyses were conducted and 11 SNPs of 4 genes were investigated to explore their associations with the PFS of NSCLC patients. Our findings showed that patients with C allele of XPD rs13181 had a poorer PFS (AC vs. CC: HR = 1.38, 95% CI = 1.10–1.73), and the T allele of XPD rs1052555 also indicated a poorer PFS (CT vs. TT vs. CC: HR = 1.97, 95% CI = 1.38–2.83).

**Heterogeneity and publication bias.** A total of 54% (n = 97) of meta-analyses showed no heterogeneity (I^2 = 0 to 25%) and 14% (n = 25) presented moderate heterogeneity (I^2 = 25 to 50%), and large heterogeneity even extreme heterogeneity existed in other meta-analyses. Sensitivity analysis and subgroup analysis were also applied to find the source of heterogeneity. The clinical heterogeneity such as disease stages, different chemotherapy regimens might be the major reason for the large or extreme heterogeneity.

We used P value for Egger's test to evaluate the potential publication bias. Our results suggested that effects of XPD rs238406 (CA + AA vs. CC), XRCC1 rs25487 (GA + AA vs. GG), XRCC1 rs1799782 (CT vs. CC) and XRCC1 rs861539 (CT vs. CC, TT vs. CC and TT + CT vs. CC) on the ORR of the ORR had significant publication bias. There was also some publication bias in the analysis of the effects of XRCC1 rs25487 (GA vs. GG, GA + AA vs. GG) on the OS. Three meta-analyses showed bias in the association of certain SNPs with PFS, including XPD rs13181 (AC vs. CC vs. AA), XPD rs1799793 (GA + AA vs. GG) and XRCC1 rs25487 (GA + AA vs. GG). More details were listed in Tables 2 and 3.

**False positive report probability.** False positive findings regarding associations between genetic variants and diseases lead to a confounding effect. Here we assessed the FPRP to determine whether our finding was noteworthy. As shown in Table 5, 23 out of 35 results had FPRP lower than 0.2, with the prior probability set as 0.1 and the FPRP was high prior probability levels (AC vs. CC vs. AA). XPD rs1799793 (GA + AA vs. GG) and XRCC1 rs25487 (GA + AA vs. GG). More details were listed in Table 5.

High-quality significant associations that emerged from the current meta-analysis were discussed below.

**Excision Repairs Cross-complementation Groups 1 (ERCC1).** Data showed that ERCC1 rs3212986 (C8092A) variant was related to the treatment response to PBC, and A allele may have poorer response comparing with C allele in Asians (A vs. CC: pooled OR = 0.71, 95% CI = 0.54–0.94). Only moderate between-study heterogeneity was observed (I^2 = 29.2%), and with a low FPRP when prior probability level was set as 0.1, suggesting that A allele of ERCC1 rs3212986 might be specifically linked to the poorer response in Asians.

ERCC1 rs11615 (C354T) was associated with OS, and T allele carriers might have unfavorable OS with HR being 1.47 and corresponding 95% CI being 1.15–1.88, and with no heterogeneity and low FPRP when prior probability level was set as 0.2. The report had low FPRP at high prior probability levels and no heterogeneity was observed. Further investigation with a larger sample size is needed to confirm the association between rs1052555 variant and prognosis of NSCLC patients.

**Xeroderma Pigmentosum Group D (XPD).** Only the dominant model was used to analyze the relation between XPD rs13181 (A2251C) mutation and OS due to insufficient raw data. We found that the variant C allele was remarkably associated with the adverse OS in overall NSCLC patients treated with PBC (AC + CC vs. AA: HR = 1.24, 95% CI = 1.07–1.44). There was no heterogeneity and publication bias in the meta-analysis, and FPRP was low with the prior probability level being 0.1. C allele was also related to poor PFS with low FPRP at the high prior probability levels (AC + CC vs. AA: HR = 1.38, 95% CI = 1.10–1.73). No heterogeneity with statistical significance was observed, but the P value for Egger's test showed that there was some publication bias in the meta-analysis. These results indicated that C allele was a risk allele for the poor clinical prognosis of NSCLC patients.

For other SNPs (rs1052555, C2133T) of XPD, we found that T allele was a risk allele and might be significantly associated with unfavorable OS (CT vs. TT vs. CC: HR = 1.71, 95% CI = 1.31–2.23). In the beginning, we included 4 articles in the meta-analysis and found that extreme heterogeneity and publication bias existed. After sensitivity analysis, we removed one article that was identified as the major source of heterogeneity, then I^2 reduced to zero and no bias was observed from these data. The report had low FPRP with the prior probability level being 0.1 or 0.01. T allele was also related to poor PFS, and pooled HR was 1.97 and the 95% CI ranged from 1.38 to 2.83, though the report had low FPRP at high prior probability levels and no heterogeneity was observed. Further investigation with a larger sample size is needed to confirm the association between rs1052555 variant and prognosis of NSCLC patients.

**Xeroderma Pigmentosum Group G (XPG).** XPG rs2296147 (T242C) might be associated with NSCLC patients' prognosis receiving platinum drugs. We found that T allele acted as a protective allele with the carriers having favorable OS (TT vs. CC: HR = 0.40, 95% CI = 0.27–0.61), no heterogeneity and publication bias was detected, and the FPRP was low both at the high (0.1) and intermediate (0.01) prior probability levels. The strength of association needs to be further studied because of the small sample size of current meta-analysis.

**X-Ray Cross-Complementing Group 1 (XRCC1).** Three genetic models were used to analyze the association between XRCC1 rs1799782 (C580T) polymorphisms and ORR, and results confirmed the positive response of patients carrying T allele to PBC with a low FPRP at the high (0.1) prior probability level, but large between-study heterogeneity existed in the three meta-analyses ((CT vs. CC: HR = 1.22, 95% CI = 1.03–1.44; I^2 = 63.4%); (TT vs. CC: HR = 1.29, 95% CI = 1.07–1.56; I^2 = 50.5%); (CT + TT vs. CC: HR = 1.22, 95% CI = 1.04–1.42; I^2 = 65.1%).
| Genetic model | Subgroup | No. of Study | Effect model | Pooled RR (95%CI) | I² (%) | P_{het} | Begg's test (P-value) | Egger's test (P-value) |
|---------------|----------|--------------|--------------|------------------|--------|--------|----------------------|-----------------------|
| ERCC1 rs3212986 | AA VS CC | Asian 7  | Fixed  | 0.71 (0.54,0.94) | 29.2  | 0.206 |          |                        |
|               |          | Caucasian 1 | Fixed  | 0.85 (0.47,1.53) | —     | —     |          |                        |
|               |          | Overall 8 | Fixed  | 0.72 (0.56,0.94) | 18.7  | 0.282 | 0.458 | 0.115                |
|               | CA VS CC | Asian 7  | Fixed  | 0.91 (0.78,1.05) | 46.3  | 0.083 |          |                        |
|               |          | Caucasian 1 | Fixed  | 1.03 (0.80,1.31) | —     | —     |          |                        |
|               |          | Overall 8 | Fixed  | 0.92 (0.80,1.05) | 41.3  | 0.103 | 0.322 | 0.259                |
|               | CA+AA VS CC | Asian 10 | Random | 0.85 (0.68,1.05) | 58.1  | 0.011 |          |                        |
|               |          | Caucasian 4 | Random | 1.19 (0.93,1.51) | 25.1  | 0.261 |          |                        |
|               |          | Overall 14 | Random | 0.95 (0.80,1.13) | 55.9  | 0.006 | 0.447 | 0.441                |
| ERCC1 rs11615 | CT VS CC | Asian 10 | Random | 0.97 (0.72,1.31) | 38.5  | 0.123 |          |                        |
|               |          | Caucasian 1 | Random | 1.03 (0.80,1.31) | —     | —     |          |                        |
|               |          | Overall 11 | Random | 0.99 (0.73,1.36) | 37.3  | 0.174 | 0.582 | 0.087                |
| XPA rs1800975 | AG VS AA | Asian 2  | Random | 2.17 (1.29,3.64) | 79.6  | 0.027 |          |                        |
|               |          | Caucasian 1 | Random | 1.01 (0.61,1.68) | —     | —     |          |                        |
|               |          | Overall 3  | Random | 1.74 (1.18,2.57) | 77.8  | 0.011 | 0.117 | 0.156                |
|               | GG VS AA | Asian 2  | Random | 1.09 (0.59,2.02) | 85.3  | 0.009 |          |                        |
|               |          | Caucasian 1 | Random | 1.22 (0.75,1.99) | —     | —     |          |                        |
|               |          | Overall 3  | Random | 1.14 (0.74,1.75) | 71.2  | 0.031 | 0.602 | 0.175                |
|               | AG+GG VS AA | Asian 3 | Random | 1.05 (0.72,1.52) | 83.8  | 0.002 |          |                        |
|               |          | Caucasian 1 | Random | 1.11 (0.68,1.80) | —     | —     |          |                        |
|               |          | Overall 4  | Random | 1.06 (0.77,1.45) | 76.0  | 0.006 | 0.174 | 0.087                |
| XPC rs2228000 | CT VS CC | Asian 3  | Fixed  | 1.09 (0.84,1.41) | 50.6  | 0.132 | 0.602 | 0.234                |
|               | TT VS CC | Asian 3  | Fixed  | 1.05 (0.71,1.56) | 29.1  | 0.244 | 0.602 | 0.989                |
|               | CT+TT VS CC | Asian 3 | Fixed | 1.09 (0.86,1.40) | 37.0  | 0.204 | 0.117 | 0.030                |
| XPC rs2228001 | AC VS AA | Asian 2  | Random | 0.85 (0.58,1.25) | 88.8  | 0.003 |          |                        |
|               | CC VS AA | Asian 2  | Random | 0.83 (0.46,1.51) | 56.1  | 0.131 |          |                        |
|               | CC+AC VS AA | Asian 3 | Random | 0.90 (0.71,1.14) | 79.1  | 0.008 | 0.602 | 0.065                |
| XPC intron9 PAT | SL VS SS | Asian 2  | Fixed  | 0.93 (0.61,1.40) | 0.0   | 0.322 |          |                        |
|               | LL VS SS | Asian 2  | Random | 1.07 (0.29,3.94) | 81.5  | 0.020 |          |                        |
|               | SL+LL VS SS | Asian 2 | Random | 0.87 (0.38,1.89) | 70.7  | 0.065 |          |                        |
| XPD rs13181  | AC VS AA | Asian 8  | Fixed  | 0.82 (0.65,1.04) | 9.80  | 0.354 |          |                        |
|               | CC VS AA | Asian 2  | Random | 1.14 (0.09,1.43) | 73.6  | 0.051 |          |                        |
|               | CC+AC VS AA | Asian 8 | Random | 1.09 (0.87,1.36) | 0.0   | 0.935 |          |                        |
|               | CA+CC VS AA | Asian 9 | Fixed  | 0.83 (0.71,0.98) | 0.0   | 0.580 |          |                        |
|               |            | Overall 20 | Fixed | 0.92 (0.82,1.03) | 0.0   | 0.615 | 1.000 | 0.414                |

Continued
| Genetic model | Subgroup | No. of Study | Effect model | Pooled RR (95%CI) | I² (%) | Phet | Begg's test (P-value) | Egger's test (P-value) |
|---------------|----------|-------------|--------------|------------------|--------|------|----------------------|-----------------------|
| AA VS GG      | Asian    | 1           | Random       | 0.20 (0.05,0.76) | —      | —    | —                   | —                     |
|               | Caucasian| 8           | Random       | 1.21 (0.96,1.51) | 0.0    | 0.551| —                   | —                     |
|               | Overall  | 9           | Random       | 1.03 (0.69,1.54) | 52.6   | 0.031| 0.144               | 0.247                 |
| GA VS GG      | Asian    | 4           | Random       | 0.88 (0.45,1.74) | 74.6   | 0.008| —                   | —                     |
|               | Caucasian| 9           | Random       | 1.04 (0.87,1.24) | 0.0    | 0.647| —                   | —                     |
|               | Overall  | 13          | Random       | 0.99 (0.81,1.23) | 35.3   | 0.100| 0.625               | 0.969                 |
| GA+AA VS GG   | Asian    | 6           | Random       | 0.83 (0.59,1.17) | 67.3   | 0.009| —                   | —                     |
|               | Caucasian| 10          | Random       | 1.04 (0.89,1.21) | 0.0    | 0.746| —                   | —                     |
|               | Overall  | 16          | Random       | 0.94 (0.79,1.11) | 40.8   | 0.046| 0.589               | 0.656                 |
| XPD rs1052555 | CT+TT VS CC | Overall 4 | Random       | 0.92 (0.65,1.31) | 67.5   | 0.026| 1.000               | 0.813                 |
| CA+AA VS CC   | Overall 3 | Fixed       | 0.96 (0.81,1.15) | 0.0    | 0.667| 0.117| 0.007a              |                       |
| XPG rs1047768 | CT VS CC | Asian 3     | Fixed        | 0.97 (0.79,1.20) | 18.8   | 0.292| —                   | —                     |
|               | Caucasian| 2           | Fixed        | 1.17 (0.88,1.55) | 0.0    | 0.777| —                   | —                     |
|               | Overall 5 | Fixed       | 1.01 (0.85,1.21) | 0.0    | 0.466| 0.624| 0.767               |                       |
| TT VS CC      | Asian 3  | Random      | 0.70 (0.27,1.81) | 87.9   | 0.000| —    | —                   | —                     |
|               | Caucasian| 2           | Random       | 0.92 (0.64,1.32) | 0.0    | 0.735| —                   | —                     |
|               | Overall 5 | Random      | 0.80 (0.49,1.32) | 76.2   | 0.002| 0.142| 0.155               |                       |
| CT+TT VS CC   | Asian 5  | Random      | 0.86 (0.61,1.21) | 68.3   | 0.013| —    | —                   | —                     |
|               | Caucasian| 2           | Random       | 1.07 (0.84,1.37) | 0.0    | 0.890| —                   | —                     |
|               | Overall 7 | Random      | 0.94 (0.75,1.19) | 55.6   | 0.036| 0.293| 0.319               |                       |
| XPG rs17655   | CG VS CC | Asian 6     | Fixed        | 1.09 (0.92,1.27) | 22.6   | 0.264| —                   | —                     |
|               | Caucasian| 1           | Fixed        | 1.00 (0.58,1.72) | —      | —    | —                   | —                     |
|               | Overall 7 | Fixed       | 1.08 (0.93,1.26) | 8.2    | 0.366| 0.453| 0.230               |                       |
| GG VS CC      | Asian 6  | Fixed       | 1.20 (0.99,1.45) | 20.1   | 0.282| —    | —                   | —                     |
|               | Caucasian| 1           | Fixed        | 1.16 (0.71,1.88) | —      | —    | —                   | —                     |
|               | Overall 7 | Fixed       | 1.19 (0.99,1.43) | 4.5    | 0.392| 0.652| 0.417               |                       |
| CG+GG VS CC   | Asian 6  | Fixed       | 1.12 (0.97,1.29) | 38.1   | 0.152| —    | —                   | —                     |
|               | Caucasian| 1           | Fixed        | 1.11 (0.68,1.80) | —      | —    | —                   | —                     |
|               | Overall 7 | Fixed       | 1.12 (0.97,1.29) | 25.7   | 0.233| 0.652| 0.495               |                       |
| XPG rs2296447 | CT VS CC | Overall 2   | Fixed        | 1.14 (0.84,1.54) | 0.0    | 0.477| —                   | —                     |
| TT VS CC      | Overall 2 | Fixed       | 1.34 (0.92,1.97) | 0.0    | 0.547| —    | —                   | —                     |
| CT+TT VS CC   | Overall 2 | Fixed       | 1.22 (0.96,1.56) | 0.0    | 0.863| —    | —                   | —                     |
| XRCCI rs25487 | GA VS GG | Overall 15  | Random       | 1.08 (0.94,1.24) | 60.8   | 0.001| 0.458               | 0.375                 |
|               | AA VS GG | Overall 15  | Random       | 1.27 (1.02,1.58) | 66.7   | 0.000| 0.216               | 0.095                 |
| GA+AA VS GG   | Overall 23| Random      | 0.89 (0.76,1.05) | 78.5   | 0.000| 0.013a| 0.004a              |                       |
| XRCCI rs1799782| CT VS CC | Overall 13  | Random       | 1.22 (1.03,1.44) | 63.4   | 0.001| 0.051               | 0.032a                |
| TT VS CC      | Overall 13| Random      | 1.29 (1.07,1.56) | 50.5   | 0.019| 1.000| 0.735               |                       |
| CT+TT VS CC   | Overall 14| Random      | 1.22 (1.04,1.42) | 65.1   | 0.000| 0.139| 0.082               |                       |
| XRCCI rs25489 | GA VS GG | Overall 2   | Fixed        | 0.99 (0.81,1.22) | 0.0    | 0.801| —                   | —                     |
| AA VS GG      | Overall 2 | Fixed       | 0.96 (0.76,1.22) | 0.0    | 0.712| —    | —                   | —                     |
| XRCC3 rs861539| CT VS CC | Asian 3     | Fixed        | 1.20 (0.94,1.53) | 0.0    | 0.588| —                   | —                     |
|               | Caucasian| 3           | Fixed        | 1.46 (1.06,1.99) | 26.3   | 0.257| —                   | —                     |
|               | Overall 6 | Fixed       | 1.51 (1.07,1.99) | 0.0    | 0.502| 0.005a| 0.009a              |                       |
| TT VS CC      | Asian 1  | Fixed       | 1.36 (0.91,2.02) | —      | —    | —    | —                   | —                     |
|               | Caucasian| 3           | Fixed        | 1.59 (1.07,2.36) | 0.0    | 0.935| —                   | —                     |
|               | Overall 4 | Fixed       | 1.48 (1.12,1.97) | 0.0    | 0.921| 0.04a| 0.001a              |                       |

Continued
| Genetic model Subgroup | No. of Study | Effect model | Pooled RR (95% CI) | I² (%) | Phet | Begg's test (P-value) | Egger's test (P-value) |
|-----------------------|-------------|--------------|-------------------|--------|------|----------------------|----------------------|
| TT + CT VS CC         | Asian 5     | Fixed        | 1.16 (0.94, 1.44) | 0.0    | 0.764 |                      |                      |
|                       | Caucasian 3 | Fixed        | 1.48 (1.10, 2.01) | 0.0    | 0.472 |                      |                      |
|                       | Overall 8   | Fixed        | 1.28 (1.07, 1.52) | 0.0    | 0.723 | 0.001*               | 0.000               |
| RRM1 rs12806698       | AA VS CC    | Overall 4    | Fixed             | 0.61   | 0.33 | 0.734               | 0.434               |
|                       | CA VS CC    | Overall 6    | Fixed             | 1.02   | 0.86 | 1.000               | 0.765               |
|                       | CA + AA VS CC Overall 6 | Fixed | 0.98 (0.83, 1.16) | 0.0    | 0.954 | 1.000               | 0.770               |
| MTHFR rs1801133       | CT VS CC    | Overall 5    | Fixed             | 0.63   | 0.44 | 0.148               | 0.327               |
|                       | TT VS CC    | Overall 5    | Random            | 0.81   | 0.38 | 0.025               | 0.327               |
|                       | CT + TT VS CC Overall 5 | Random | 0.66 (0.37, 1.18) | 64.8   | 0.023 | 0.624               | 0.598               |
| GSTP1 rs1695          | AG VS AA    | Asian 5      | Random            | 1.19   | 0.92 | 0.004               |                      |
|                       |             | Caucasian 2  | Random            | 0.94   | 0.62 | 0.529               |                      |
|                       |             | Overall 7    | Random            | 1.14   | 0.91 | 0.012               | 0.881               |
|                       | GG VS AA    | Asian 4      | Random            | 1.17   | 0.71 | 0.001               |                      |
|                       |             | Caucasian 2  | Random            | 0.73   | 0.28 | —                   | —                   |
|                       |             | Overall 5    | Fixed             | 1.45   | 1.20 | 0.416               | 1.000               |
|                       | AG + GG VS AA | Asian 11  | Random            | 1.47   | 1.11 | 0.000               |                      |
|                       |             | Caucasian 2  | Random            | 0.90   | 0.59 | 0.713               |                      |
|                       |             | Overall 13   | Random            | 1.37   | 1.06 | 0.000               | 0.625               |
| MDR1 rs1045642        | CT VS CC    | Asian 3      | Fixed             | 0.69   | 0.50 | 0.495               |                      |
|                       |             | Caucasian 2  | Fixed             | 0.81   | 0.52 | 0.421               |                      |
|                       |             | Overall 5    | Fixed             | 0.73   | 0.56 | 0.678               | 0.624               |
|                       | TT VS CC    | Asian 3      | Fixed             | 0.47   | 0.26 | 0.252               |                      |
|                       |             | Caucasian 2  | Fixed             | 0.62   | 0.32 | 0.093               |                      |
|                       |             | Overall 5    | Fixed             | 0.52   | 0.34 | 0.061               | 0.142               |
|                       | CT + TT VS CC | Asian 5     | Fixed             | 0.61   | 0.48 | 0.050               |                      |
|                       |             | Caucasian 2  | Fixed             | 0.75   | 0.49 | 0.551               |                      |
|                       |             | Overall 7    | Fixed             | 0.64   | 0.52 | 0.722               | 0.652               |
| CDA rs2072671         | AC VS AA    | Asian 1      | Fixed             | 1.48   | 0.78 | 0.281               |                      |
|                       |             | Caucasian 2  | Fixed             | 0.85   | 0.56 | 0.183               |                      |
|                       |             | Overall 3    | Fixed             | 0.99   | 0.70 | 0.062               | 0.829               |
|                       | CC VS AA    | Asian 2      | Random            | 0.62   | 0.10 | 0.065               |                      |
|                       |             | Caucasian 2  | Random            | 0.77   | 0.36 | 0.064               |                      |
|                       |             | Overall 3    | Random            | 0.95   | 0.53 | 0.055               | 0.602               |

**Table 2.** The association between candidate gene polymorphisms and objective response. *Begg's test \( P < 0.05; \) **Egger's test \( P < 0.05.\)

**X-Ray Cross-Complementing Group 3 (XRCC3).** Results from subgroup meta-analysis sorted by ethnicity showed that T allele of XRCC1 rs861539 (C241T) was associated with the positive response of PBC treatment in Caucasian population, three genetic models had consistent results (CT VS CC: \( RR = 1.46, 95\% CI = 1.06–1.99; \) TT VS CC: \( RR = 1.59, 95\% CI = 1.07–2.36; \) TT + CT VS CC: \( RR = 1.48, 95\% CI = 1.10–2.01), no heterogeneity has been found. Begg's test and Egger's test revealed that some publication bias existed in the meta-analysis. However, Lower FRPR values suggested that the findings were statistically significant. Genetic variant of XRCC1 rs861539 was not associated with OS and PFS in the current meta-analysis.

**Methylenetetrahydrofolate Reductase (MTHFR).** T allele of MTHFR rs1801133 (C665T) might be related to the negative response, the report had low FRPR at the high (0.1) prior probability level, with pooled HR = 0.63, 95% CI = 0.44–0.89, \( I^2 = 41.0\% \) when comparing CT and CC genotypes. The other genetic models including TT vs. CC and CT + TT vs. CC didn't show statistical significance.

**Glutathione S-transferase P1 (GSTP1).** For GSTP1 rs1695 (A313G), two genetic models showed consistent results about the association of the SNP with response (GG vs. AA: \( HR = 1.45, 95\% CI = 1.20–1.74; \) AG + GG vs. AA: \( HR = 1.37, 95\% CI = 1.06–1.76), the same effects were also observed in the Asian group by subgroup analysis in model AG + GG vs. AA (HR = 1.47, 95% CI = 1.11–1.95). However, we did not find a significant association in
| Genetic model | No. of Study | Effect model | Pooled HR (95%C.I) | I2% | Phet (P-value) | Egger's test (P-value) |
|--------------|-------------|--------------|-------------------|-----|---------------|------------------------|
| ERCC1        |             |              |                   |     |               |                        |
| rs3212986    |             | Fixed        | 2.06 (1.19,3.57)  | 49.9| 0.112         | 0.174 0.270            |
| AA VS CC     | 4           | Fixed        | 1.16 (0.83,1.63)  | 16.5| 0.310         | 0.327 0.622            |
| CA VS CC     | 5           | Fixed        | 0.97 (0.63,1.50)  | 81.1| 0.000         | 0.851 0.356            |
| CA+AA VS CC  | 6           | Random       |                   |     |               |                        |
| AC VS AA     | 3           | Fixed        | 1.20 (0.81,1.79)  | 0.0 | 0.526         | 0.602 0.644            |
| CC VS AA     | 3           | Fixed        | 1.20 (0.66,2.18)  | 0.0 | 0.437         | 0.117 0.151            |
| XPA rs1800975|             | Random       |                   |     |               |                        |
| AG+GG VS AA  | 2           | Fixed        | 0.97 (0.73,1.29)  | 85.3| 0.009         |                        |
| XPC rs2228009|             | Random       |                   |     |               |                        |
| CT VS CC     | 2           | Fixed        | 0.74 (0.37,1.48)  | 85.5| 0.009         |                        |
| TT VS CC     | 2           | Fixed        | 0.91 (0.56,1.50)  | 0   | 0.449         |                        |
| CT+TT VS CC  | 2           | Random       | 0.77 (0.40,1.48)  | 84.9| 0.010         |                        |
| XPD rs1052555|             | Random       |                   |     |               |                        |
| CT VS CC     | 2           | Fixed        | 1.10 (0.89,1.37)  | 0.0 | 0.426         | 0.573 0.251            |
| TT VS CC     | 8           | Random       | 1.40 (0.92,2.16)  | 60.1| 0.014         | 1.000 0.796            |
| CT+TT VS CC  | 5           | Fixed        | 1.47 (1.15,1.88)  | 0.0 | 0.682         | 0.624 0.597            |
| XPD rs1799793|             |             |                   |     |               |                        |
| AA VS GG     | 5           | Random       | 1.09 (0.62,1.92)  | 65.3| 0.021         | 0.624 0.595            |
| GA VS GG     | 4           | Fixed        | 0.78 (0.62,0.99)  | 0.0 | 0.419         | 0.497 0.422            |
| GA+AA VS GG  | 6           | Random       | 1.29 (0.94,1.76)  | 66.8| 0.010         | 0.851 0.759            |
| XPD rs238406 |             | Fixed        | 1.26 (0.95,1.68)  | 0.0 | 0.913         |                        |
| CT VS CC     | 2           | Random       | 1.11 (0.69,1.79)  | 59.3| 0.117         |                        |
| TT VS CC     | 3           | Random       | 1.11 (0.45,2.78)  | 89.9| 0.000         | 0.602 0.326            |
| XPG rs1047768|             | Random       |                   |     |               |                        |
| CT VS CC     | 3           | Fixed        | 0.98 (0.73,1.32)  | 0.0 | 0.743         |                        |
| TT VS CC     | 3           | Fixed        | 1.02 (0.68,1.51)  | 0.0 | 0.394         |                        |
| CT+TT VS CC  | 3           | Fixed        | 0.86 (0.68,1.08)  | 19.4| 0.265         |                        |
| XPG rs17655  |             | Fixed        |                   |     |               |                        |
| CT VS CC     | 3           | Fixed        | 0.79 (0.59,1.05)  | 0.0 | 0.920         | 0.602 0.376            |
| TT VS CC     | 3           | Fixed        | 0.40 (0.27,0.61)  | 13.3| 0.315         | 0.117 0.333            |
| XPG rs873601 |             | Fixed        |                   |     |               |                        |
| AG VS AA     | 3           | Fixed        | 0.91 (0.69,1.21)  | 0.0 | 0.548         | 1.000 0.878            |
| GG VS AA     | 3           | Fixed        | 0.67 (0.46,0.97)  | 0.5 | 0.366         | 0.602 0.710            |
| XRCC1 rs25487|             | Random       |                   |     |               |                        |
| GA VS GG     | 13          | Random       | 0.87 (0.71,1.07)  | 70.3| 0.000         | 0.038 0.029a           |
| AA VS GG     | 11          | Random       | 0.84 (0.52,1.36)  | 80.1| 0.000         | 0.186 0.183            |
| GA+AA VS GG  | 6           | Random       | 0.96 (0.68,1.36)  | 68.8| 0.007         | 0.039 0.019b           |
| XRCC1 rs1799782|           |             |                   |     |               |                        |
| CT VS CC     | 7           | Fixed        | 0.91 (0.76,1.08)  | 0.0 | 0.784         | 0.362 0.233            |
| TT VS CC     | 7           | Fixed        | 0.81 (0.63,1.04)  | 0.0 | 0.424         | 0.453 0.685            |
| XRCC1 rs25489|             | Fixed        |                   |     |               |                        |
| GA VS GG     | 2           | Fixed        | 0.85 (0.63,1.15)  | 41.3| 0.192         |                        |
| AA VS GG     | 2           | Fixed        | 1.31 (0.65,2.65)  | 22.6| 0.256         |                        |
| CT VS CC     | 3           | Fixed        | 0.95 (0.76,1.17)  | 0.0 | 0.630         | 0.117 0.064            |
| TT VS CC     | 3           | Fixed        | 1.01 (0.72,1.41)  | 46.1| 0.156         | 0.602 0.935            |
| TT+CT VS CC  | 2           | Fixed        | 0.83 (0.61,1.13)  | 0.0 | 0.661         |                        |

Continued
In this study, we described the meta-analysis findings of associations between genetic polymorphisms and treatment outcomes of NSCLC patients receiving platinum drugs. Our study identified that 14 SNPs in 10 genes were significantly associated with the ORR, OS and PFS. We further calculated FPRPs of the statistically significant results and 23 results were identified with high-quality evidence (Table 5).

Discussion

In this study, we described the meta-analysis findings of associations between genetic polymorphisms and treatment outcomes of NSCLC patients receiving platinum drugs. Our study identified that 14 SNPs in 10 genes were statistically associated with clinical prognosis including treatment response, OS and PFS. We further calculated FPRPs of the statistically significant results and 23 results were identified with high-quality evidence (Table 5).

The anti-cancer activity of platinum agents mainly depends on the formation of DNA adducts which inhibit DNA replication, hinder cell division and induce cell apoptosis. DNA repair pathways including nucleotide excision repair (NER) and base excision repair (BER) could timely repair the damaged DNA induced by platinum agents and thus lead to treatment failure. DNA repair pathways or certain physiological functions. As shown in Fig. 2, they included DNA repair pathway (EXCC1, ERCC1, XPD, XPG and XRCC1), drug influx and efflux (MDR1), metabolism and detoxification (GSTM1) and DNA synthesis (MTHFR).

| Genetic model | No. of Study | Effect model | Pooled HR (95%CI) | I2% | P_{het} | Begg's test (P-value) | Egger's test (P-value) |
|--------------|-------------|--------------|------------------|-----|---------|----------------------|-----------------------|
| RRM1 rs12806698 | AA VS CC | Fixed | 0.86 (0.47, 1.58) | 0.0 | 0.977 | | |
| | AG VS CC | Fixed | 0.91 (0.66, 1.24) | 0.0 | 0.513 | | |
| | AC+AA VS CC | Random | 1.01 (0.71, 1.42) | 66.7 | 0.029 | 0.174 | 0.391 |
| GSTP1 rs1695 | AG VS AA | 8 Random | 1.03 (0.82, 1.28) | 52.9 | 0.038 | 0.383 | 0.113 |
| | GG VS AA | 5 Random | 0.87 (0.51, 1.47) | 71.2 | 0.008 | 0.624 | 0.535 |
| | AG+GG VS AA | 2 Fixed | 1.19 (0.92, 1.55) | 0.0 | 0.538 | | |
| MDR1 rs1045642 | CT VS CC | 3 Fixed | 0.91 (0.64, 1.29) | 0.0 | 0.883 | 0.117 | 0.173 |
| | TT VS CC | 3 Fixed | 0.91 (0.64, 1.29) | 0.0 | 0.883 | 0.117 | 0.173 |
| CDA rs2072671 | AC VS CC | 2 Fixed | 0.90 (0.63, 1.29) | 0.0 | 0.334 | | |
| | CC VS AA | 2 Random | 1.80 (0.47, 6.87) | 80.6 | 0.023 | | |

Table 3. The association between candidate gene polymorphisms and OS. *Begg's test P < 0.05; †Egger's test P < 0.05.

Multidrug resistance 1 (MDR1). There were statistically significant associations between MDR1 rs1045642 (T3435C) polymorphism and treatment response in both overall and Asian groups in three comparison genetic models (CT vs. CC, TT vs. CC, CT+TT vs. CC), and results are presented in Table 2. Three statistically significant findings with low FPRP were considered as noteworthy (CT vs. CC: overall RR = 0.73; 95% CI = 0.56–0.94; CT+TT vs. CC: Asian RR = 0.61, 95% CI = 0.48–0.79; CT+TT vs. CC: overall RR = 0.64, 95% CI = 0.52–0.80). Significant between-study heterogeneity and potential bias were not observed in all comparison models.

Biological pathways associated with platinum drugs treatment outcomes in NSCLC patients. Genetic variants significantly associated with treatment outcomes of NSCLC patients receiving platinum drugs had impacts on several biological pathways or certain physiological functions. As shown in Fig. 2, they included DNA repair pathway (EXCC1, ERCC1, XPD, XPG and XRCC1), drug influx and efflux (MDR1), metabolism and detoxification (GSTM1) and DNA synthesis (MTHFR).

Discussion

In this study, we described the meta-analysis findings of associations between genetic polymorphisms and treatment outcomes of NSCLC patients receiving PBC had impacts on several biological pathways or certain physiological functions. As shown in Fig. 2, they included DNA repair pathway (EXCC1, ERCC1, XPD, XPG and XRCC1), drug influx and efflux (MDR1), metabolism and detoxification (GSTM1) and DNA synthesis (MTHFR).
and cancer. We identified that the T allele was related to a negative response of PBC. *MDR1* gene encodes for P-glycoprotein (P-gp), which plays a major role in the process of drug efflux and influx across the cell membrane. We found that *MDR1* rs1045642 variant was associated with ORR only in Asians, and published meta-analyses supported the association. GST is a phase II metabolic enzyme involved in the platinum detoxification, mediated by glutathione (GSH) conjugation. Increasing GSH content would decrease platinum-DNA binding and result in platinum resistance. *GSTP1* gene was found to be associated with platinum treatment response, and our results indicated that T allele of *GSTP1* rs1695 increased the ORR in NSCLL patients, but the association was only observed in Asians. A previous meta-analysis also reported the same effect as ours.

Great efforts have been made to identify the molecular predictive markers of platinum sensitivity. By further integrating our results according to genes biological functions, we found that the majority of polymorphisms of those genes significantly associated with treatment outcomes of platinum agents were involved in four biological pathways or physiological functions. According to the mechanism of platinum, DNA repair pathway may play a key role in the response of platinum therapy. Our results showed that the important components of DNA repair pathways (*ERCC1, XPD, XPG, XRCC1* and *XRCC3*) were involved in the efficacy of platinum treatment and clinical outcome of NSCLL patients. *MDR1* and *GSTP1*, which were related to drug transportation and detoxification respectively, influenced the outcome of platinum treatment. Another potential key gene was *MTHFR*, which was involved in regulating folate metabolism and DNA synthesis and was correlated with platinum sensitivity.

In the current meta-analysis, we comprehensively searched the relevant articles and explored all the eligible genes related to multiple biological functions, aiming to provide an updated and more critical summary of the available evidence of genetic polymorphisms and treatment outcomes of PBC in NSCLC patients. We first analyzed six SNPs including *ERCC1* rs2298881, *XPD* rs1052555, *XPD* rs238406, *XPG* rs17655, *XPG* rs2296147 and *XPG* rs873601. There is a high chance that an initial “statistically significant” finding based on *P* value alone turns out to be a false-positive finding, so we calculated the FPRP of each statistically significant association to ensure the credibility of our findings, and we identified 11 SNPs in 9 genes that might truly associate with the ORR and/or OS and/or PFS of NSCLC patients receiving platinum drugs.

However, there were some limits in the present meta-analysis. First, despite the intensive efforts we have made to comprehensively search the related studies, some information might have been missed. Second, between-study...
heterogeneity existed in the current meta-analysis. Although sensitivity analysis and subgroup analysis were applied to find the source of heterogeneity, some heterogeneity couldn’t be fully explained by statistical methods. Clinical heterogeneity might play a role in the large between-study heterogeneity, such as disease stage and age.

Table 5. FPRP values for the SNPs associated with the response, OS and PFS of NSCLC patients receiving platinum-based chemotherapy. *FPRP value < 0.2.

| Genetic/SNP | Genetic model | Subgroup | No. of study | Pooled RR of ORR (95% CI) | Reported P-value | Power | FPRP based on prior |
|-------------|---------------|----------|--------------|---------------------------|------------------|-------|-------------------|
| **ERCC1 rs3212986** | AA VS CC | Asian | 7 | 0.71 (0.54,0.94) | 0.017 | 0.670 | 0.184* |
| | AA VS CC | Overall | 8 | 0.72 (0.56,0.94) | 0.016 | 0.714 | 0.166* |
| **XRCC3 rs861539** | CT VS CC | Caucasian | 3 | 1.46 (1.06,1.99) | 0.017 | 0.568 | 0.208 |
| | CT VS CC | Overall | 6 | 1.31 (1.07,1.59) | 0.006 | 0.915 | 0.058* |
| | TT VS CC | Caucasian | 3 | 1.59 (1.07,2.36) | 0.021 | 0.386 | 0.332 |
| | TT VS CC | Overall | 4 | 1.48 (1.12,1.97) | 0.007 | 0.537 | 0.108* |
| | TT+CT VS CC | Caucasian | 3 | 1.48 (1.10,2.01) | 0.012 | 0.534 | 0.169* |
| | TT+CT VS CC | Overall | 8 | 1.28 (1.07,1.52) | 0.005 | 0.965 | 0.043* |
| **XPA rs1800975** | AG VS AA | Asian | 2 | 2.17 (1.29,3.64) | 0.003 | 0.081 | 0.270 |
| | AG VS AA | Overall | 3 | 1.74 (1.18,2.57) | 0.005 | 0.228 | 0.175* |
| **XPD rs13181** | CA+CC VS AA | Asian | 11 | 0.83 (0.71,0.98) | 0.028 | 0.995 | 0.202 |
| | AA VS GG | Asian | 1 | 0.20 (0.05,0.76) | 0.047 | 0.069 | 0.861 |
| **XRCCI rs25487** | AA VS GG | Overall | 15 | 1.27 (1.02,1.58) | 0.032 | 0.932 | 0.236 |
| **XRCCI rs1799782** | CT VS CC | Overall | 13 | 1.22 (1.03,1.44) | 0.019 | 0.993 | 0.145* |
| | TT VS CC | Overall | 13 | 1.29 (1.07,1.56) | 0.009 | 0.940 | 0.076* |
| | CT+TT VS CC | Overall | 14 | 1.22 (1.04,1.42) | 0.010 | 0.996 | 0.085* |
| **MTHFR rs1801133** | CT VS CC | Overall | 5 | 0.63 (0.44,0.89) | 0.009 | 0.374 | 0.174* |
| **GSTP1 rs1695** | AG+GG VS AA | Asian | 11 | 1.47 (1.11,1.95) | 0.008 | 0.556 | 0.109* |
| | CT VS CC | Overall | 13 | 1.37 (1.06,1.76) | 0.014 | 0.761 | 0.140* |
| | TT VS CC | Overall | 5 | 0.73 (0.56,0.94) | 0.015 | 0.759 | 0.148* |
| | CT+TT VS CC | Overall | 7 | 0.64 (0.52,0.80) | 0.000 | 0.360 | 0.002* |
| **MDRI rs1045642** | CT+TT VS CC | Asian | 5 | 1.47 (1.15,1.88) | 0.002 | 0.564 | 0.033* |
| | CT+TT VS CC | Overall | 5 | 1.47 (1.15,1.88) | 0.002 | 0.564 | 0.033* |
| **ERCC1 rs31615** | CT+TT VS CC | Overall | 5 | 0.69 (0.50,0.95) | 0.023 | 0.584 | 0.261 |
| **ERCC1 rs3212986** | AA VS CC | Overall | 4 | 2.06 (1.19,3.57) | 0.050 | 0.129 | 0.411 |
| **XPD rs13181** | AC+CC VS AA | Overall | 8 | 1.24 (1.07,1.44) | 0.005 | 0.994 | 0.042* |
| **XPD rs1799793** | GA VS GG | Overall | 4 | 0.78 (0.62,0.99) | 0.041 | 0.902 | 0.291 |
| **XPD rs1052555** | CT+TT VS CC | Overall | 3 | 1.71 (1.31,2.23) | 0.000 | 0.167 | 0.004* |
| **XPG rs873601** | GG VS AA | Overall | 3 | 0.67 (0.46,0.97) | 0.034 | 0.511 | 0.374 |
| **XPG rs2296147** | TT VS CC | Overall | 3 | 0.40 (0.27,0.61) | 0.000 | 0.009 | 0.021* |
| **XPD rs13181** | AG+CC VS AA | Overall | 4 | 1.38 (1.10,1.73) | 0.005 | 0.765 | 0.058* |
| **XPD rs1052555** | CT+TT VS CC | Overall | 2 | 1.97 (1.38,2.83) | 0.000 | 0.070 | 0.030* |

Figure 2. Biological pathways and physiological functions influenced by genetic variants which were statistically significantly associated with clinical outcomes of platinum-based chemotherapy in NSCLC patients.
Third, three genotypic variant (heterozygote variant vs. wild type, homozygote variant vs. wild type and the dominant model) were used for this study, the other models including recessive model and allele comparison were not performed because of limited raw data. However, the models used in the study were commonly used in genetic analysis, and could in part decrease the type I error inflation. Fourth, we didn’t analyze the role of gene-gene as well as gene-environment interactions in the modification of chemotherapy efficacy, and attention should be paid to these factors in further studies.

In conclusion, this collection of data might provide a useful platform for research and clinical healthy practice. Further work still needs to be done to pinpoint the use of these SNPs as prognostic biomarkers for assessing objective response and progression risk in NSCLC patients receiving platinum-based regimens.

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**Author Contributions**

L.M.T. and Z.Q.L. conceived and designed the study. L.M.T., C.F.Q., T.Z. and Y.X.J. acquired the data, performed data extraction. L.M.T. analyzed the data. L.M.T. wrote the paper. X.L., J.Y.Y., W.Z. and H.H.Z. provided valuable comments and important insights.

**Additional Information**

**Competing Interests:** The authors declare that they have no competing interests.

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