Supplementary data section for: Association of TPMT, COMT and ACYP2 variants with cisplatin induced ototoxicity in a UK cohort of paediatric cancer patients

# Methods, Supplemental Digital Content S1

Supplementary Table S1 CTCAE and Chang grading scales for ototoxicity



ain cases of asymmetric hearing loss the better ear determined the final grade

b in cases of asymmetric hearing loss the worse ear determined the final grade

**c**in cases where 8 kHz had not been tested, 6 kHz readings were accepted instead

# Systematic Review and Meta-Analysis

Supplementary Table S2: Systematic Review Search Strategy

|  |
| --- |
| Systematic Review Search Strategy |
| pharmacogenetic\* OR pharmacogenomic\* OR genetic risk factor OR SNP OR single nucleotide polymorphism\* OR genetic mutation\* OR GWAS OR genom\* analysis AND cisplatin OR CDDP OR cisplatinumANDhearing loss OR deafness OR ototoxicity OR audiometryAND Infant[MeSH] OR Infant\* OR infancy OR Newborn\* OR Baby\* OR Babies OR Neonat\* OR Preterm\* OR Prematur\* OR Postmatur\* OR Child[MeSH] OR Child\* OR Schoolchild\* OR School age\* OR Preschool\* OR Kid or kids OR Toddler\* OR Adolescent[MeSH] OR Adoles\* OR Teen\* OR Boy\* OR Girl\* OR Minors[MeSH] OR Minors\* OR Puberty[MeSH] OR Pubert\* OR Pubescen\* OR Prepubescen\* OR Pediatrics[MeSH] OR Paediatric\* OR Paediatric\* OR Peadiatric\* OR Schools[MeSH] OR Nursery school\* OR Kindergar\* OR Primary school\* OR Secondary school\* OR Elementary school\* OR High school\* OR Highschool\* |

All papers identified in the search were uploaded to the online software Covidence and two reviewers (CB and ALJ) independently screened the papers for inclusion. Any conflicts were resolved by discussion at a meeting between CB and ALJ, at which the final list of included papers was decided upon. Methodological quality of the papers was assessed using the quality assessment checklist for pharmacogenetic studies previously published by Jorgensen and Williamson (5). In addition, data on the following was extracted from each study and stored in an excel spreadsheet: year of publication, ethnicity of participants, SNPs investigated, outcomes investigated including their definition, sample size, and study design.

In the event that more than one study investigated association between the same SNP and outcome combination, data required to undertake a meta-analysis was extracted from those studies. This included the following, where available: numbers in each genotype group, number of cases and controls per genotype group, odds ratio, standard error of odds ratio, confidence interval for odds ratio. The data was then synthesised within a meta-analysis using the software package Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and the results of the meta-analysis presented in a forest plot. Since different papers had undertaken analyses assuming different modes of inheritance, and due to the variability between studies in how data was reported, it was only possible to conduct a meta-analysis where the allelic odds ratio was calculated (i.e. the odds ratio of developing ototoxicity for the mutant allele vs wild-type allele). The statistical method used to estimate a pooled odds ratio across studies was the Mantel-Haenszel random-effects method (6) and heterogeneity was assessed by referring to the I2 statistic (7, 8). No formal adjustment for study quality was made in the meta-analyses, however results of assessing methodological quality were considered when exploring potential sources of heterogeneity.

# RESULTS

Figure, Supplemental Digital Content S2: CONSORT Chart of the recruitment process

Data insufficient to differentiate between Chang 1b and 2A

Patients recruited to MAGIC study at time of analysis

(n=149)

Incomplete clinical data (n=6)

Complete clinical data (n=143)

Insufficient audiograms to grade hearing (n=23)

Interpretable audiograms (n=120)

Patients able to undergo Chang grading of hearing (n=119)

Patients able to undergo CTCAE grading of hearing (n=120)

Table, Supplementary digital content S3: *COMT and TPMT* genetic variants association using worse ear grade and dichotomised outcomes; results of the multivariable logistic regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | CTCAE grade 0 vs. 1-4 | CTCAE grade 0 vs. 2-4 | CTCAE grade 0 vs. 3+4 |
| SNP (reference) | Estimate (se) | P-valuea | Adjusted P-valued | Estimate (se) | P-valueb | Adjusted P-valued | Estimate(se) | P-valuec | Adjusted P-valued |
| *COMT* |  |  |  |  |  |  |  |  |  |
| rs9332377 (CC) | 0.061 (0.44) | 0.89 | 1.00 | -0.19(0.47) | 0.69 | 1.00 | -0.21(0.57) | 0.71 | 1.00 |
| rs4646316 (CC) | 0.058 (0.48) | 0.90 | 1.00 | 0.012(0.49) | 0.98 | 1.00 | -0.35(0.62) | 0.58 | 1.00 |
| *TMPT* |  |  |  |  |  |  |  |  |  |
| rs12201199 (AA) | -1.41(0.60) | 0.020 | 0.10 | -1.54(0.66) | 0.019 | 0.095 | -1.85(0.84) | 0.028 | 0.14 |
| rs1142345 (TT) | -0.73 (0.63) | 0.25 | 1.00 | -0.85(0.68) | 0.21 | 1.00 | -1.13(0.90) | 0.21 | 1.00 |
| rs1800460 (CC) | -0.28(0.69) | 0.68 | 1.00 | -0.41 (0.73) | 0.58 | 1.00 | 0.38 (1.01) | 0.71 | 1.00 |

Table, Supplementary Digital Content S4: *COMT and TPMT* genetic variants association using better ear grade and ordinal outcomes; results of multivariable ordinal logistic regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
| SNP (reference) | Estimate (SE) | Overall P-valuea | Adjusted P- valueb |
| *COMT* rs9332377 (CC)*Grade 1 vs Grade 0:**Grade 2 vs Grade 0:**Grade 3 vs Grade 0:* *Grade 4 vs Grade 0:* | -1.14 (1.49)-0.37 (0.45)-1.16 (0.65)-0.16 (1.62) | 0.40 | 1.00 |
| rs4646316 (CC) | 0.62 (1.13)0.38 (0.49)0.0093 (0.58)1.30 (1.62) | 0.86 | 1.00 |
| *TPMT* rs12201199 (AA) | -16.8 (4860)-0.40 (0.58)-2.11 (0.94)-17.5 (4700) | 0.07 | 0.35 |
|  rs1142345 (TT) | -16.7 (6060)0.058 (0.62)-1.90 (1.19)-15.7 (6340) | 0.24 | 1.00 |
| rs1800460 (CC) | -16.2 (8070)0.36 (0.68)-19.1 (7230)-15.7 (4970) | 0.13 | 0.65 |

* aDetermined by multivariable ordinal logistic regression model adjusting clinical factors: sex, cranial irradiation, total dose of cisplatin, vincristine and carboplatin
* bDetermined using Bonferroni-corrected P value, compared to a significance threshold of P < 0.05

Table, Supplementary Digital Content S5: *COMT and TPMT* genetic variants association using better ear grade and dichotomised outcomes; results of the multivariable logistic regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | CTCAE grade 0 vs. 1-4 | CTCAE grade 0 vs. 2-4 | CTCAE grade 0 vs. 3+4 |
| SNP (reference) | Estimate (se) | P-valuea | Adjusted P-valued | Estimate (se) | P-valueb | Adjusted P-valued | Estimate(se) | P-valuec | Adjusted P-valued |
| *COMT* |  |  |  |  |  |  |  |  |  |
| rs9332377 (CC) | -0.55 (0.40) | 0.17 | 0.85 | -0.58(0.41) | 0.16 | 0.80 | -1.20(0.70) | 0.088 | 0.44 |
| rs4646316 (CC) | 0.27 (0.44) | 0.54 | 1.00 | 0.31(0.44) | 0.49 | 1.00 | 0.16 (0.62) | 0.80 | 1.00 |
| *TMPT* |  |  |  |  |  |  |  |  |  |
| rs12201199 (AA) | -0.94(0.56) | 0.097 | 0.49 | -0.88(0.57) | 0.12 | 0.60 | -1.91(1.04) | 0.067 | 0.34 |
| rs1142345 (TT) | -0.49 (0.61) | 0.42 | 1.00 | -0.43(0.61) | 0.48 | 1.00 | -1.61(1.31) | 0.22 | 1.00 |
| rs1800460 (CC) | -0.21(0.67) | 0.75 | 1.00 | -0.16 (0.67) | 0.82 | 1.00 | -15.1 (1680) | 0.99 | 1.00 |

1. Determined by adjusting clinical factors (cranial irradiation, p-value: 0.00001; carboplatin, p-value: 0.0009) in multivariablte logistic regression models
2. Determined by adjusting clinical factors (cranial irradiation, p-value: 0.0001; carboplatin, p-value: 0.0026) in multivariable logistic regression models
3. Determined by adjusting clinical factors (age, p-value: 0.026; cranial irradiation, p-value: 0.059; sex, p-value: 0.044; vincristine, p-value: 0.029) in multivariable logistic regression models
4. Determined using Bonferroni-corrected p values

Table, Supplementary Digital Content S6: *ACYP2* genetic variant association using worse ear grade and dichotomised outcomes; results of the multivariable logistic regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Chang 0 vs.1a-4 | Chang 0 vs. 2a-4 | Chang 0 vs.3+4 |
| SNP (reference) | Estimate (se) | P-valueb |  | Estimate (se) | P-valuec |  | Estimate(se) | P-valued |  |
| *ACYP2* |  |  |  |  |  |  |  |  |  |
| rs1872328 (GG) | 0.40(1.20) | 0.73 |  | -15.8(1460) | 0.99 |  | -15.3(1460) | 0.99 |  |

1. Determined by adjusting clinical factors (cranial irradiation, p-value: 0.0007; carboplatin, p-value: 0.011) in multivariable logistic regression models
2. Determined by adjusting clinical factors (age, p-value: 0.0065; cranial irradiation, p-value: 0.00002; carboplatin, p-value: 0.0089) in multivariable logistic regression models
3. Determined by adjusting clinical factors (age, p-value: 0.069; cranial irradiation, p-value: 0.0001; carboplatin, p-value; 0.0035) in multivariable logistic regression models

Table, Supplementary Digital Content S7: *ACYP2* genetic variant association using better ear grade and ordinal outcomes; results of the multivariable logistic regression analysis.

|  |  |  |
| --- | --- | --- |
| rs1872328 (GG) | Estimate (SE) | Overall P-valuea |
| *Grade 1a vs Grade 0:**Grade 1b vs Grade 0:**Grade 2a vs Grade 0:* *Grade 2b vs Grade 0:* *Grade 3 vs Grade 0:* *Grade 4 vs Grade 0:* | **2.11 (1.33)****2.62 (1.51)****-18.9 (27500)****-18.9 (26100)****-19.5 (24300)****-1.77 (16700)** | 0.13 |

aDetermined by multivariable ordinal logistic regression model adjusting clinical factors: total dose of cisplatin, cranial irradiation and carboplatin

Table, Supplementary Digital Content S8: *ACYP2* genetic variant association using better ear grade and dichotomised outcomes; results of the multivariable logistic regression analysis

|  |  |  |  |
| --- | --- | --- | --- |
|  | Chang 0 vs.1a-4 | Chang 0 vs. 2a-4 | Chang 0 vs.3+4 |
| SNP (reference) | Estimate (se) | P-valueb |  | Estimate (se) | P-valuec |  | Estimate(se) | P-valued |  |
| rs1872328 (GG) | 0.99(1.19) | 0.41 |  | -15.4(1460) | 0.99 |  | -12.96(1455) | 0.99 |  |

Figure, Supplementary Digital Content S9: Systematic Review Quorum Flow Chart of the reviewing process

Records identified through database searching (n=270)
(n = 270)

## Screening

## Included

## Eligibility

## Identification

Duplicates removed (n = 14)

Records screened
(n = 256)

Records excluded
(n = 245)

Pre-clinical (n=118)

Reviews/Not Genetic (n=44)

Adult data (n=42)

Not Cisplatin (n=18)

Not ototoxicity (n=13)

Not genes of interest (n=10)

Full-text articles assessed for eligibility (n=11)
(n = 22 )

Full-text articles excluded (n=4)

Studies included in qualitative synthesis
(n = 7)

Table, Supplementary Digital Content S10: Methodological Quality of included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Hagleitner** | **Lanvers-Kaminsky** | **Pussegoda** | **Ross** | **Yang** | **Xu** | **Vos** |
|  | **Dutch cohort** | **Spanish cohort** |  |  | **Discovery cohort** | **Replication cohort** | **Cohort A** | **Cohort B** | **Discovery cohort** | **Validation cohort** |  |
| **1. Choosing the genes/SNPs to genotype** |  |  |  |  |  |  |  |  |  |  |  |
| Was a literature review undertaken and the findings summarized ? | partially | partially | partially | partially | partially | partially | partially | partially | partially | partially | Partially |
| Are reasons given for choosing the genes and SNPs genotyped ? | yes | yes | yes | yes | yes | yes | yes | yes | na-GWAS | yes | Yes |
| If reasons include previous association studies are key details from these provided? | no | no | no | no | na | na | no | no | na | na | Yes |
| If reasons include functional studies are supporting data provided? | na | na | na | na | na | na | na | na | na | na | na |
| Is method to adjust for multiple testing described ? | no | no | no | no | yes | yes | no | no | yes - GWAS threshold applied | no | na |
| Are precise p-values provided for all associations? | yes | no | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| **2. Sample size** |  |  |  |  |  |  |  |  |  |  |  |
| What is the sample size ? | 110 | 38 | 63 | 155 | 53 | 109 | 213 | 41 | 238 | 68 | 156 |
| Are details given of how the sample size was calculated? | no | no | no | no | no | no | no | no | no | no | no |
| Are details given of the a priori power to detect effect sizes of varying degrees? | no | no | no | yes | no | no | no | no | no | no | yes |
| **3. Study design**  |   |   |   |   |   |   |   |   |   |   |   |
| What is the study design? | retrospective cohort | retrospective cohort | retrospective cohort | case/control | case/control | case/control | retrospective cohort | retrospective cohort | retrospective cohort | retrospective cohort | retrospective cohort |
| If study is case–control are the two groups clearly defined? | na | na | na | yes | yes | yes | na | na | na | na | na |
| If study is case-control were they genotyped in mixed batches? | na | na | no | nk | nk | nk | na | na | na | na | na |
| **4. Reliability of genotypes** |  |  |  |  |  |  |  |  |  |  |  |
| Is the genotyping procedure described?  | yes | yes | no | yes | yes | yes | yes | yes | yes | no | yes |
| Are the primers described?  | no | no | no | no | no | no | yes | yes | no | no | no |
| Were quality control methods used and described? | no | no | no | partially | no | yes | yes | yes | yes | yes | yes |
| Were findings from quality control methods, if used, described ? | na | na | na | yes | na | yes | yes | yes | yes | yes | no |
| Are any genotype frequencies previously reported quoted ? | no | no | no | no | no | no | yes | yes | no | no | no |
| Were genotyping personnel blinded to outcome status? | nk | nk | nk | nk | yes | yes | no | no | no | no | nk |
| If human inference required was this independently undertaken by at least two people ? | na | na | na | na | na | na | na | na | na | na | na |
| **5. Missing genotype data** |  |  |  |  |  |  |  |  |  |  |  |
| Is extent of missing data summarized? | yes | yes | no | no (but samples with call rate<95% excluded) | no (but samples with call rate<95% excluded) | no (but samples with call rate<95% excluded) | no | no | no - but only thosepassing QC included in sample size  | no - but only thosepassing QC included in sample size  | no |
| Where extent is summarized are reasons for missing data given? | no | no | na | na | na | na | na | na | na | na | na |
| Are checks for missingness at random reported?  | no | no | no | no | no | no | no | no | no | no | no |
| Is missing genotype data imputed?  | no | no | no | no | no | no | no | no | no | no | no |
| Does paper quote number of patients contributing to each analysis? | yes | yes | yes | yes | yes | yes | yes | yes | no | yes | yes |
| If paper does quote number of patients contributing to analyses does this agree to sample size? | no | no | yes | yes | yes | yes | yes | yes | na | yes | no |
| **6. Population stratification** |   |   |   |   |   |   |   |   |   |   |   |
| Are tests undertaken for cryptic population stratification? | no | no | no | yes | yes | yes | no | no | yes | yes | no |
| If so, are results quoted? | na | na | na | yes | yes | yes | na | na | yes | yes | na |
| Is cryptic population stratification adjusted for in the analyses? | no | no | no | yes | yes | yes | no | no | yes | yes | no |
| **7. Hardy–Weinberg Equilibrium (HWE)** |  |  |  |  |  |  |  |  |  |  |  |
| What test is undertaken to check for HWE?  | nk | nk | nk | Permutation test | Permutation test | Permutation test | Chi-squared/Fisher | Chi-squared/Fisher | nk | nk | nk |
| Where test undertaken, is p-value threshold applied to determine deviation from HWE quoted? | no | no | na | no | yes | yes | no | no | na | na | no |
| Where test undertaken, are SNPs deviating from HWE highlighted? | yes - says none deviate | yes - says none deviate | na | no | no - just say were removed  | no - just say were removed  | yes | yes | na | na | yes(none deviate) |
| Where test undertaken, and some SNPs found to deviate, are steps taken to explore deviation from HWE reported? | na | na | na | na | no | no | no | no | na | na | na |
| Where test undertaken, and some SNPs found to deviate, are deviating SNPs excluded from further analysis? | na | na | na | na | yes | yes | yes | yes | na | na | na |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **8. Mode of inheritance** |  |  |  |  |  |  |  |  |  |  |  |
| Is a specific mode of inheritance assumed? If so which ? | yes - additive and allelic (in MA) | yes -allelic (in MA) | yes - none and dominant | Methods say OR calculated for Hets and MT homos, but in results only one OR quoted per SNP | yes - none and additive | yes - none and additive | additive, but also sensitivity analyses under none/recessive/dominant (data not shown but states consistent) | additive, but also sensitivity analyses under none/recessive/dominant (data not shown but states consistent) | additive | additive | yes, dominant |
| Is justification provided for assumptions made regarding mode of inheritance (if no mode or a specific mode is assumed)? | no | no | no | no | no | no | no | no | no | no | no but there are no MT homo |
| If no mode of inheritance is assumed does the paper explain limitations of this? | na | na | na | na | na | na | na | na | na | na | na |
| If several analyses undertaken under different assumptions are they adjusted for multiple testing? | na | na | no | na | nk-Bonferroni applied for number of tests but unclear if this included different modes of inheritance) | nk-Bonferroni applied for number of tests but unclear if this included different modes of inheritance) | na as classed as sensitivity analyses | na as classed as sensitivity analyses | na | na | na |
| **9. Choice and definition of outcomes** |   |   |   |   |   |   |   |   |   |   |   |
| Does the paper clearly define all outcomes investigated? | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Is justification provided for the choice of outcomes? | yes | yes | no | no | no | no | no | no | no | no | no |
| Are results shown for all outcomes mentioned?  | yes | no | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| **10. Compliance to treatment** |   |   |   |   |   |   |   |   |   |   |   |
| Is compliance to treatment measured? | no | no | no | no | no | no | no | no | no | no | no |
| If compliance is measured are adjustments for non-compliance made in the analyses? | na | na | no | na | na | na | na | na | na | na | na |

**Appendix, Supplementary Digital Content S11: Results of assessing methodological quality of studies included in the systematic review and meta-analyses**

Although the systematic review resulted in seven included studies, in total this resulted in 11 different cohorts as four of the studies comprised two separate cohorts. Of these 11, eight were retrospective cohorts (2, 3, 9-11) and three were case-control (12, 13). Cases and controls were defined clearly in the three case-control studies; however, it is not clear from the papers whether the two groups were genotyped in different batches or not. There is a risk that the quality of genotyping will differ between the two groups, and hence the introduction of bias, if cases and controls are genotyped separately.

Sample size for all cohorts was small, ranging from 38 to 238 and therefore there is high possibility that some of the cohorts were underpowered to detect a statistically significant association with the SNPs investigated even if a true association exists. Disappointingly, none of the studies provided details of how their required sample size was estimated, although two studies (11, 12) gave details of the power they had a priori to detect effect sizes of varying degrees.

There was clarity across all studies in terms of justification for the choice of SNPs investigated, therefore there is little risk of selective reporting of genetic variants. However, it is disappointing that in seven cohorts (2, 3, 9, 10, 12), even though association with more than one SNP is investigated, adjustment is not made for multiple testing and therefore the type I error rate will be inflated in these studies.

The genotype procedure is described in all but two cohorts, however genotype quality control procedures is not described for four cohorts (9, 10, 13). For those assessing quality, the results of that assessment were provided for all but one cohort (11). For those where quality control procedures are not described it is difficult to assess the reliability of the genotype data. The approach used to test for deviation from Hardy-Weinberg Equilibrium (HWE) is described only in five cohorts (3, 12, 13) but for one of these cohorts (12) the results of the test are not provided. For a further three cohorts (9, 11) it is reported that no SNPs deviated from HWE.

Missing genotype data was mentioned in all but three cohorts (3, 10, 11), however the extent of missing data and reasons for missingness was not provided for any of the cohorts. In one of the studies (11) where missing genotype data was not mentioned, the number of samples contributing to the analyses was not consistent with the sample size. Further, none of the studies mentioned undertaking checks for missingness at random or any attempts at imputing missing data. If data is missing and this is not at random this can lead to bias.

Different assumptions regarding the underlying mode of inheritance are made across the cohorts, with some cohorts reporting analyses undertaken under more than one assumption. For one cohort (12) however, the methods section states that separate odds ratios will be calculated for both heterozygotes and mutant homozygotes, whilst only one odds ratio is reported. Consequently, it is difficult to ascertain what the odds ratio represents in this cohort. Justification for choice of mode of inheritance is not provided in any of the studies and therefore there is a risk of selective reporting whereby analyses under several difference assumptions about mode of inheritance were undertaken and only the most statistically significant reported. For one of the cohorts (10) where analyses under more than one assumption are reported, no adjustment is made for multiple testing whilst in another two cohorts (13), although Bonferroni adjustment is mentioned, it is not clear whether this relates to the multiple tests undertaken under different assumptions about mode of inheritance. There is therefore a risk that the type I error rate is inflated in these cohorts.

Cryptic population stratification is assessed and adjusted for in five cohorts (2, 12, 13). Analyses which do not consider cryptic population stratification are at potential risk from confounding due to the underlying mixed population.

Outcomes and their definitions are clearly defined in all cohorts, although justification for choice of outcome is only provided for two (9). Where no justification is provided for choice of outcome there can be an associated risk of selective reporting of outcomes where several outcomes or outcome definitions are investigated with only the most statistically significant reported. In addition, for one cohort (9), results are not provided for some of the outcomes described.

Finally, although desirable in pharmacogenetics studies, none of the included cohorts mention assessing for adherence with treatment.

1. Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. Journal of Clinical Oncology. 2010;28(10):1788-95.

2. Xu H, Robinson GW, Huang J, Lim JY-S, Zhang H, Bass JK, et al. Common variants in ACYP2 influence susceptibility to cisplatin-induced hearing loss. Nature genetics. 2015.

3. Yang JJ, Lim JY-S, Huang J, Bass J, Wu J, Wang C, et al. The Role of Inherited TPMT and COMT Genetic Variation in Cisplatin‐Induced Ototoxicity in Children With Cancer. Clinical Pharmacology & Therapeutics. 2013;94(2):252-9.

4. Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. Archives of pediatrics & adolescent medicine. 2008;162(2):111-6.

5. Jorgensen AL, Williamson PR. Methodological quality of pharmacogenetic studies: issues of concern. Statistics in medicine. 2008;27(30):6547-69.

6. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library; 2008.

7. Higgins J, Thompson SG. Quantifying heterogeneity in a meta‐analysis. Statistics in medicine. 2002;21(11):1539-58.

8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.

9. Hagleitner MM, Coenen MJ, Patino-Garcia A, de Bont ES, Gonzalez-Neira A, Vos HI, et al. Influence of Genetic Variants in TPMT and COMT Associated with Cisplatin Induced Hearing Loss in Patients with Cancer: Two New Cohorts and a Meta-Analysis Reveal Significant Heterogeneity between Cohorts. PloS one. 2014;9(12):e115869.

10. Lanvers‐Kaminsky C, Malath I, Deuster D, Ciarimboli G, Boos J, Zehnhoff‐Dinnesen A. Evaluation of Pharmacogenetic Markers to Predict the Risk of Cisplatin‐Induced Ototoxicity. Clinical Pharmacology & Therapeutics. 2014;96(2):156-7.

11. Vos HI, Guchelaar H-J, Gelderblom H, de Bont ES, Kremer LC, Naber AM, et al. Replication of a genetic variant in ACYP2 associated with cisplatin-induced hearing loss in patients with osteosarcoma. Pharmacogenetics and genomics. 2016;26(5):243-7.

12. Pussegoda K, Ross CJ, Visscher H, Yazdanpanah M, Brooks B, Rassekh SR, et al. Replication of TPMT and ABCC3 Genetic Variants Highly Associated With Cisplatin‐Induced Hearing Loss in Children. Clinical Pharmacology & Therapeutics. 2013;94(2):243-51.

13. Ross CJ, Katzov-Eckert H, Dubé M-P, Brooks B, Rassekh SR, Barhdadi A, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nature genetics. 2009;41(12):1345-9.