TITLE PAGE

Title: The role of germline variants in chemotherapy outcome in brain tumors: a systematic review of pharmacogenetic studies.

Running head: Pharmacogenetics of chemotherapy outcome in brain tumors.

Authors: M.J. Klumpers¹, M.J.H. Coenen², C.E.M. Gidding¹, D.M.W.M. Te Loo¹

¹ Department of Pediatric Oncology, Department of Pediatrics, Radboud university medical center, Nijmegen, The Netherlands.

² Radboud university medical center, Radboud Institute for Health Sciences, Department of Human Genetics, Nijmegen, The Netherlands.

Corresponding author: M.J.H. Coenen, Radboud university medical center, Radboud Institute for Health Sciences, Department of Human Genetics, PO Box 9101, 6500 HB Nijmegen, the Netherlands; e-mail: Marieke.Coenen@radboudumc.nl

Key words: brain tumors, chemotherapy, pharmacogenetics

Word count:

Abstract:	120
Article:	3,745
Figures and tables:	784
Supplementary:	730

23 **ABSTRACT**

24 This systematic review provides an overview of publications concerning pharmacogenetic
25 research in pediatric patients with medulloblastoma and low-grade glioma. Three electronic
26 databases searches including a manual search were performed to identify studies investigating
27 potential interactions between germline variants and chemotherapy efficacy and toxicity. Of
28 3,570 citations, twenty-one studies were included. Outcomes include overall survival,
29 progression-free survival and treatment related adverse events ($N = 5$), cisplatin-induced
30 ototoxicity ($N = 13$) and vincristine-induced neurotoxicity ($N = 3$). This review shows that the
31 number of pharmacogenetic studies in well-defined pediatric brain tumor cohorts is poor and
32 studies often report conflicting results. Large-scale international collaborations allowing
33 analysis of sufficiently sized cohorts are therefore very important for the future of personalized
34 medicine in brain tumors.

INTRODUCTION

Brain tumors are the most common solid malignancies of childhood, with incidence rates of 3-5 per 100,000 children per year in the western population.[1, 2] The majority of pediatric brain tumors are low-grade gliomas and medulloblastomas.[3] Low-grade gliomas (WHO-classification grade I and II) derive from glial cells in the central nervous system and are considered less aggressive with favorable survival rates of 85-95%.[4] Medulloblastomas are primary neuroectodermal tumors with survival rates varying between 30% and 80%, depending on risk group and age.[5-9] Despite these types of brain tumors to be clinically very different, they are treated with comparable chemotherapeutic regimens, including the cornerstone agents cisplatin, carboplatin, vincristine and cyclophosphamide. Unfortunately, brain tumor patients often suffer from long term sequelae partly due to tumor specific features like location and size, and partly due to treatment related side effects.

Chemotherapy made it possible in several treatment protocols to postpone radiotherapy or decrease its dose or target volume, thereby decreasing radiotherapy side effects and, furthermore, increase survival.[10, 11] Despite the advances of chemotherapy, patients show a great variety in response to chemotherapeutic agents. Not only concerning anti-tumor effect, but also in the development and severity of toxicities. Chemotherapy-related side effects play a major role in reduced quality of life.[12] The most disabling long-term side effects caused by the chemotherapy include ototoxicity, nephrotoxicity, decreased cognitive functions and neurotoxicity.[13, 14] Ototoxicity is most often caused by treatment with cisplatin or carboplatin, which can result in an impairment of daily functioning and cognitive development.[15, 16] In addition, these platinum-based agents can, especially when combined with cyclophosphamide, lead to an increased risk of nephrotoxicity. Vincristine, a drug commonly used in pediatric cancer practice, is known to induce serious peripheral neurotoxicity during treatment. Severe toxicities are still often a reason for chemotherapy dose adjustments, which leads to a reduction of the desired anti-tumor effect and, consequently, might influence treatment efficacy.

Efforts have been made to reduce the toxic side effects of chemotherapy in children to prevent them from long-term sequelae. For example, amifostine addition may be protective against cisplatin-induced ototoxicity.[17, 18] However, due to the lack of large randomized controlled trials testing its protective effect and a meta-analysis reporting no statistically significant results, amifostine is not included in clinical guidelines.[19] Clinical differences, e.g. age and cumulative chemotherapy dose, are known to play a role in the variable response to chemotherapy, but do not sufficiently predict the occurrence of severe side effects.[20, 21] For this reason, no clinical or biological markers for chemotherapy response are available for upfront stratification of patients with a brain tumor. Gaining more insight in the cause of the variations in response to chemotherapy and being able to predict response might help to optimize chemotherapeutic treatment for these patients and might prevent them from low treatment efficacy and drug-related adverse events. A tool to gain this insight is pharmacogenetics.

Pharmacogenetic studies aim to identify inherited germline genetic markers that are associated with drug response, including treatment efficacy and drug-related adverse events. Associations found in pharmacogenetic research can be used for creating predictive models, offering tailored therapy and might thereby lead to improved survival and prevention from severe toxicities. This study field has already shown promising results in oncology patients. For example, multiple pharmacogenetic studies have shown a link between variants in the *DPYD* gene and high risk of severe toxicities during treatment with fluoropyrimidines, one of the most frequently prescribed group of anticancer drugs.[22-24] In the field of pediatric oncology, genetic variants associated with the outcome of acute lymphoblastic leukemia (ALL) are extensively investigated. An example is the role of polymorphisms in the glutathione-S transferase family, e.g. *GSTM1*, in the response to chemotherapy in treatment of ALL.[25] Pharmacogenetic studies have been published investigating patients with other types of cancer being exposed to the same chemotherapeutic agents as brain tumor patients, e.g. vincristine in ALL patients.[26] However from a pharmacogenetic view, brain tumors distinguish

89 themselves from other pediatric cancers because of the presence of multiple possible
90 confounding factors. These factors may include for example hearing loss secondary to cranial
91 radiotherapy and decreased cognitive function as a result of tumor localization and size. Also,
92 chemotherapeutic regimens (including cumulative dose) do often vary depending on the type
93 of cancer. Therefore, it might be difficult to directly translate the findings to other (pediatric)
94 cancer patients to brain tumor patients.

95 This systematic review is a collection of pharmacogenetic studies investigating the response
96 to chemotherapy in pediatric patients with a medulloblastoma or low-grade glioma. This review
97 provides an overview of the current state of studies in this research area and may present a
98 more distinct lead for future studies.

99 MATERIALS AND METHODS

100 Studies were included if they investigated associations between germline polymorphisms and
101 treatment outcome of chemotherapy in medulloblastoma and low-grade glioma patients. The
102 cornerstone agents used in current treatment regimens, being cisplatin, carboplatin, vincristine
103 and cyclophosphamide, plus the additional agents etoposide and lomustine were included in
104 the search. Treatment outcome was defined as chemotherapy efficacy, being overall survival
105 (OS) or progression free survival (PFS), or chemotherapy-related toxicity. Studies investigating
106 the mentioned chemotherapeutic agents in heterogeneous cohorts with multiple pediatric
107 cancers including brain tumors were also selected. Studies in patients with an anaplastic
108 glioma (grade III) or glioblastoma (grade IV) were excluded, because of treatment regimens
109 with other chemotherapeutic agents.

110 The electronic databases MEDLINE, Embase, and Cochrane Library were systematically
111 searched for relevant publications without limitations concerning publication dates. This was
112 performed with the help of a medical librarian. The date of search was 30th of October, 2016.
113 Detailed search terms are presented in **Supplementary Table 1**. Two reviewers (MK and MC)
114 independently screened the list of citations for eligible articles. Potential citations were
115 reviewed by their titles; selected titles were reviewed by abstract and, if the abstract was
116 eligible, by full-text. After systematic screening, the reference lists of the included articles were
117 manually screened for additional potential articles that may have been missed with the initial
118 search strategy. Discrepancies between the two reviewers concerning eligibility of the studies
119 did not occur. Case reports, conference abstracts and articles not written in English were
120 excluded, as well as studies investigating associations with genetic variants in tumor cells.

RESULTS

The systematic search yielded a total of 3,570 unique citations, of which twenty-one studies were included in the review (**Figure 1**). The majority of the included studies used a candidate gene approach. Also, one pathway approach study and one genome-wide association study (GWAS) were identified. Pharmacogenetic studies regarding carboplatin, cyclophosphamide, etoposide and lomustine were not found. The included studies could be sorted into three categories; studies investigating the role of variants in overall treatment outcome of patients with brain tumors and studies specifically looking into relations between inherited variants and cisplatin-induced ototoxicity and vincristine-induced neurotoxicity. Here, the results of these studies will be presented and described by category.

Pharmacogenetics and overall treatment outcome

Five out of the twenty-one included studies focused on the role of pharmacogenetics with overall treatment outcome of chemotherapy in patients with medulloblastoma or low-grade glioma. Most studies investigated the influence of variations in specific genes on survival and presence of adverse events during treatment. It is important to note that treatment efficacy, e.g. OS and PFS, is not only determined by the chemotherapeutic treatment, but also by clinical variables, intrinsic tumor characteristics and other treatment facets. Despite this fact, survival is often used as an endpoint in pharmacogenetic studies into chemotherapy outcome to assess the overall impact of a genetic variation on treatment efficacy. When a study is performed with candidate genes that are known to influence specific drug pharmacokinetics and -dynamics, one may suspect a relation between this genetic variant and a significant difference in treatment outcome. Details of the included studies are visualized in **Table 1**, which shows that these candidate approach studies have mainly investigated detoxification genes.

Genetics variants in members of the glutathione S-transferase (*GST*) family are investigated in three studies, focusing on the relation of these variants with OS, PFS and risk of drug-related adverse events in brain tumor patients.[27-29] *GST* polymorphisms were studied because the enzymes encoded by these genes have a known function in detoxification of several types of chemotherapy, including alkylating and platinum agents, which are used in brain tumor treatment. A study in 42 medulloblastoma patients reported associations with both *GSTM1* and *GSTT1* null genotypes and any $\geq$ grade 3 toxicity (including myelosuppression, neurotoxicity, ototoxicity and nephrotoxicity) and intellectual impairment.[28] Variants in *GST pi 1* (*GSTP1*) were studied in 106 medulloblastoma/PNET patients, identifying the variant *GSTP1* 105A>G to be significantly associated with hearing loss.[29] The mentioned associations in *GST* were not identified in an earlier study in a large cohort of various primary malignant gliomas (n=278, which consisted of forty-four low-grade gliomas, but zero medulloblastomas).[27] Replication studies concerning these associations in brain tumor patients have not appeared. No significant associations between variants in *GST* and PFS or OS were found in these studies.

Pharmacogenetics and cisplatin-induced ototoxicity

Thirteen papers reported on pharmacogenetics concerning cisplatin-induced hearing loss, including one GWAS, in a total of 649 brain tumor patients. An overview of the published articles is provided in **Table 2**. The first published pharmacogenetic studies investigating cisplatin-induced ototoxicity in brain tumor patients were small-sized candidate approach studies in mixed cohorts of pediatric cancer patients.[30-33] Several *GST* variants were studied by Peters *et al.*, leading to the identification of the association between *GSTM3*B* and a lower chance of cisplatin-induced ototoxicity in a small heterogeneous cancer cohort (n=39, of which 3 brain tumor patients).[30] These associations were never investigated in brain tumor patients only. Four studies, including one pathway approach study, investigated variants in the gene Megalin (*LRP2*), which was studied because of its known expression in the marginal cells of the stria vascularis in the inner ear.[33-36] The study by Riedemann *et al.* found an

association between the A allele of *LRP2* rs2075252 and a higher risk for development of ototoxicity in various pediatric cancer patients,[33] but this finding was not replicated by others.[34-36] Likewise, Choeprasert *et al.* identified an association between *LRP2* rs2228171 and hearing loss, which was not in line results published in the other studies.[33-36]

Two newly investigated candidate genes, being *SLC22A2* and *SOD2*, were found to be significantly linked to ototoxicity. Lanvers-Kaminsky *et al.* found the polymorphism *SLC22A2* rs316019 G>T to be a protective marker for hearing loss in 64 pediatric patients (of which 12 brain tumor patients) and replicated this result in 66 adults with solid tumors.[37] The *SLC22A2* was studied because it encodes a transporter which is likely to be involved in cisplatin-induced oto- and nephrotoxicity. A study by Brown *et al.* recently reported the C allele of *SOD2* rs4880 to be significantly associated with increased susceptibility to ototoxicity in 71 medulloblastoma and PNET patients.[38] Five variants in this candidate gene were investigated because of their association with platinum toxicity in renal epithelial cells and its relation with noise-induced hearing loss. Replication studies of the results for *SLC22A2* and *SOD2* have not been published to date.

A pharmacogenetic study using a pathway approach was performed by Ross *et al.* in a cohort of 162 pediatric cancer patients, including 33 brain tumor patients.[35] The authors studied 1,949 variants in 220 drug metabolizing genes. The variants *TPMT* rs12201199 and *COMT* rs9332377 were detected to be significantly associated with cisplatin-induced hearing loss. The association between *TPMT* rs12201199 and hearing loss was replicated in a cohort consisting of 155 additional pediatric cancer patients (of which 37 brain tumor patients). Combined analysis of both patient groups also lead to an additional identification of an association between *ABCC3* rs1051640 and hearing loss.[39] However, the results of a study by Yang *et al.* were not in line with the previous findings, reporting no association of *TPMT* or *COMT* with ototoxicity, both *in vitro* (using mice with different *TPMT* genotypes) and *in vivo* (213 medulloblastoma patients).[40] Also, three recent publications were unable to detect

associated variants in *TPMT* and *COMT* to cisplatin-induced hearing loss in brain tumor patients.[36, 41, 42] The conflicting results of these studies suggest that these genetic variants may not be suitable for clinical application.

The only published GWAS in pediatric brain tumor patients so far was performed by Xu *et al.* in 2015. They investigated associations with 1,716,999 variants in 218 children with embryonal brain tumors, including 203 medulloblastoma patients.[41] The genetic variant rs1872328 in *ACYP2* reached genome-wide significance, showing patients who were carrying of the A allele of this variant all developed hearing loss. Similar results were found in the replication cohort which included 68 brain tumor patients.

Pharmacogenetics and vincristine-induced neurotoxicity

The role of genetic variants in the response to vincristine are only investigated in three small scale candidate gene studies in cohorts consisting of patients with various pediatric cancers, including a handful of brain tumor patients (**Table 3**). The studies investigated genetic variants in *ABCB1*, *CYP3A4* and *CYP3A5*, but they were unable to identify associations with vincristine pharmacokinetics and vincristine-induced neurotoxicity.[43-45]

DISCUSSION

This systematic review provides an overview of publications concerning pharmacogenetic research in pediatric medulloblastomas and low-grade gliomas, to evaluate existing evidence of the role of genetic variants to chemotherapy treatment outcome. As pharmacogenetics is poorly investigated in homogenous brain tumor populations, studies in pediatric solid tumor cohorts partially consisting of brain tumor patients were also reviewed. However, these results should be interpreted with caution, as interpatient variation concerning disease and treatment may be confounding variables for genetic association analysis, and thus may limit the predictive capacity of these variants in pediatric medulloblastomas and low-grade gliomas.

A few studies investigated the influence of genetic variants on survival as an endpoint for treatment efficacy. As mentioned before, survival is not only determined by chemotherapy efficacy, and therefore, in contrast to drug-related adverse events, other (clinical) variants need to be taken in great consideration when interpreting such an endpoint. Well-defined cohorts are therefore very important. Members of the detoxifying family *GST* have been a point of interest in pharmacogenetic studies in brain tumor patients concerning survival.[27-29] These genes encode for enzymes which catalyse the conjugation of glutathione of multiple toxic chemicals, which leads to inactivation. In other words, high *GST* enzyme activity is associated with drug resistance, which may lead to lower treatment efficacy and, consequently, lower survival rates. The drugs known to be influenced by *GST* members include alkylating and platinum agents and their metabolites, but also the free radicals formed by chemotherapy and radiation.[46, 47] Despite this hypothesis, genetic variants in *GST* genes did not significantly influence OS and PFS investigated in studies in low-grade gliomas and medulloblastomas.[27-29] One study included in this review did find a significant association between *GST* and survival. However the association was only present in the subgroup of anaplastic gliomas (WHO-classification grade III), which are treated with a different regimen compared to the brain tumors we focussed on.[27] Because of this difference, the results in anaplastic gliomas do probably not apply directly to low-grade gliomas and medulloblastomas.

The majority of pharmacogenetic studies in brain tumor patients have focussed on cisplatin-related ototoxicity. Cisplatin is a widely used chemotherapeutic agent in oncology, for treatment of e.g. pediatric brain tumors and osteosarcomas, and adult testicular, ovarian and non-small cell lung cancers. Especially children are at great risk of developing cisplatin-induced ototoxicity, which occurs in up to 60% of the pediatric patients.[48, 49] Brain tumor patients are even at higher risk, because the majority of these patients also receive cranial radiation, which is an additional risk factor for hearing loss.[50, 51] Because cisplatin is routinely used, numerous studies have appeared investigating prevention methods (e.g. medical interventions), as well as identification of clinical or genetic predictors to prevent this disabling side effect.[52] However to date, no upfront stratification methods for cisplatin-induced ototoxicity are used in daily practise.

Members of the *GST* family have not only been point of interest concerning their possible influence on treatment efficacy, but also their relation with cisplatin-induced ototoxicity. As mentioned earlier, GST enzymes are known to influence the level of drug resistance to platinum-based agents and have an effect on free radicals. Concerning ototoxicity, low GST activity is associated with low drug inactivation and thereby high levels of metabolites and free radicals, possibly leading to damage of the cochlea. One study in medulloblastoma patients reported that carriers of the G allele on position 105 in the coding sequence of *GSTP1* have an increased risk of hearing loss after cisplatin treatment.[29] In contrast, Oldenburg *et al.* found an increased risk of ototoxicity in patient carrying the A allele in this *GSTP1* variant in 173 adult testicular cancer survivors.[53] Also, no associations with genetic variants in *GSTP1* were identified in three studies in pediatric solid cancers (including the pathway approach study by Ross *et al.*).[30, 35, 36] However, the majority of patients in these cohorts did not receive cranial radiation, which is a confounding factor for ototoxicity and, therefore, might influence the results of the genetic association analysis. The earlier mentioned GWAS, also performed in medulloblastomas patients, does not report this polymorphism to be associated with cisplatin-induced hearing loss.[41]

270 A variant in the gene *ACYP2* seems very promising to predict cisplatin induced hearing loss,
271 which was discovered in a GWAS in medulloblastoma patients by Xu *et al.*[41] In this study,
272 all patients carrying the A allele in rs1872328 developed hearing loss upon cisplatin treatment.
273 The exact working mechanism of the variant is not elucidated yet, but *ACYP2* is known to be
274 expressed in the cochlea.[54] Nonetheless, this is in our view a promising candidate for clinical
275 implementation as in our replication study in osteosarcoma patients, again all patients with the
276 A allele developed hearing loss. These findings suggest that the variant might also be useful
277 to predict cisplatin-induced hearing loss in other tumors treated with this agent.[55]
278 Unfortunately, the frequency of the variant is not high, thus only a small part of the patients
279 that have a high risk for hearing loss can be identified.

280 The polymorphisms *TPMT* and *COMT* and their role in cisplatin-induced hearing loss have
281 been extensively studied in pediatric oncology patients, including brain tumor patients. Due to
282 inconsistent results of multiple study groups, the effect of these variants is still
283 controversial.[35, 36, 39-42, 56] These inconsistencies could be a result of differences in for
284 example audiometry or study population and thereby, findings are not generally applicable. In
285 addition, the direct mechanism between these variants and ototoxicity is still unclear, which
286 makes it difficult to value the findings thus far.

287 The role of pharmacogenetics in vincristine, known for its high risk of neurotoxicity, is poorly
288 investigated in brain tumor patients, despite the fact that it is often the reason for chemotherapy
289 dose limitations in these patients. Pharmacogenetic studies to vincristine-induced toxicities
290 have been more extensively performed in patients with ALL, leading to the identification of the
291 relation between *CYP3A5* and vincristine-induced neurotoxicity.[57, 58] However, other
292 studies failed to confirm these findings,[26, 59, 60] including studies in solid tumors discussed
293 in this review.[44, 45]

294 Recently, a GWAS by Diouf *et al.* identified a polymorphism in the promoter region of the gene
295 *CEP72* associated with an increased risk on and severity of vincristine-related neurotoxicity in

321 patients with ALL.[26] The results were backed-up with *in vitro* experiments showing an influence of *CEP72* expression on the neurons and leukemia cells derived from human stem cells and their sensitivity to vincristine. These results were replicated in adult ALL patients, but no associations were found in a study in a Spanish cohort with pediatric ALL patients.[61, 62] However, the mentioned studies investigated neurotoxicity development during different treatment phases, being during the continuation and induction phase, respectively. To date, no publications focussing on *CEP72* polymorphisms and its role in the development of vincristine-induced toxicities in brain tumor patients have appeared. Because it is hypothesised that the potential interaction between the germline *CEP72* polymorphisms and vincristine is comparable in different cancer types, it would be very interesting to perform replication studies in other vincristine-treated malignancies, including brain tumors. Because vincristine is a widely used agent, this might lead to a broad clinical application of these findings.

Concluding remarks

This review revealed that the pharmacogenetic research area in brain tumors is mainly performed in heterogeneous pediatric cancer cohorts. In contrast to other pediatric malignancies including osteosarcoma and ALL [55, 63], the number pharmacogenetic studies in well-defined cohorts of exclusively brain tumor patients is poor. Without a homogeneous study population and validation of findings in a sufficiently large population, clinical implementation of pharmacogenetic results is not within reach yet. Though we believe that the *ACYP2* and *CEP72* genes are very good candidates to study in additional patient cohorts with the ultimate goal, after proper validation, implementation in the clinical setting.

The majority of pharmacogenetic studies in brain tumors focused on one or a few candidate genes. A genome wide approach is an appropriate method to discover novel unexpected variants, but also to identify various variants which have limited effects on their own but together play a big role in final response to therapy. The number of GWASs is lagging behind

322 in the pediatric (brain) tumor population, considering the fact only one GWAS has been
323 performed to date. This can probably be attributed to the small patient cohorts available for
324 pharmacogenetic association studies. Large cohorts are required to create enough power to
325 identify relevant variants using a GWAS, which emphasizes the need for national and
326 international collaboration for brain tumor research. These homogeneous cohorts are not only
327 needed for identification, but also for replication and (prospective) validation of associated
328 genes, which are essential steps before clinical implementation is possible. In addition, the
329 pharmacogenetic field is also moving to next generation sequencing to identify genetic variants
330 or mutations linked to treatment outcome, for which large cohorts are even more essential.
331 Sufficiently sized cohorts and large scale screening methods will result in more insight in
332 interpatient treatment variability, and may lead to clinical application of pharmacogenetic
333 knowledge. Preferably, genetic association results should be backed-up with functional studies
334 to unravel the working mechanisms of the findings. Of course, not the complete spectrum of
335 treatment outcome can be predicted by pharmacogenetics. Also tumor properties (e.g. somatic
336 mutations or tumor methylation patterns) can be the reason for a poor outcome. Ultimately,
337 these factors in combination with pharmacogenetics will enable optimal personalized treatment
338 of pediatric brain tumor patients, which should be reflected in improved survival and less side-
339 effects.

340 **CONFLICTS OF INTEREST**

341 The authors declare no conflicts of interest.

342

343 **ACKNOWLEDGMENT**

344 This review is supported by the Foundation of Childhood Cancer, Nijmegen ("Stiching
345 Vrienden KOC").

Figure 1: Flowchart of study selection

Table 1: Characteristics of studies of treatment efficacy and toxicity in brain tumor patients

First author[Ref]	Year	Study approach	No. of MB/ LGG patients	MB/ LGG	Ethnic origin; nationality	Gene(s) investigated	Outcome measures	Associated variant(s)	(Possible) functional role of the genetic variant
Okcu[27]	2004	Candidate gene approach	n = 44 (of 278)	LGG	Non-Hispanic white; American	<i>GSTM1</i> <i>GSTT1</i> <i>GSTP1</i>	OS, toxicities	None	NA
Barahmani[28]	2008	Candidate gene approach	n = 42	MB	Hispanic, non-Hispanic white, African American, unspecified; American	<i>GSTM1</i> <i>GSTT1</i>	PFS, toxicities, intellectual impairment	<i>GSTT1 null</i> <i>GSTM1 null</i>	Enzyme activity ↓
Rednam[29]	2013	Candidate gene approach	n = 89 (of 106)	MB	Non-Hispanic white, Hispanic, other; American	<i>GSTP1</i>	PFS, OS, toxicities	<i>GSTP1</i> 105 A>G	Enzyme activity ↓
Jin[64]	2016	Candidate gene approach	n = 147 (of 269)	LGG	NS; Chinese	<i>IL4</i> <i>IL13</i> <i>IL10</i> <i>IL4R</i>	PFS, OS	<i>IL4R</i> r1801275	Unkown

[illegible]

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; OS, overall survival; PFS, progression-free survival; NA, not applicable; NS, not specified.

Table 2: Characteristics of studies of cisplatin-induced ototoxicity in patients with brain tumors

First author [Ref]	Year	Study approach	No. of MB/ LGG patients	MB/ LGG	Ethnic origin; nationality	Gene(s) investigated	Associated variant(s)	(Possible) functional role of the genetic variant
Peters[30]	2000	Candidate gene approach	n = 3 (of 39) ^a	MB	NS; German	<i>GSTM1</i> <i>GSTM3</i> <i>GSTT1</i> <i>GSTP1</i> <i>GSTZ1</i>	<i>GSTM3*B</i>	Enzyme activity ↑
Peters[31]	2003	Candidate gene approach	n = 3 (of 39) ^a	MB	NS; German	Mutations in mtDNA	None	NA
Knoll[32]	2006	Candidate gene approach	n = 7 (of 11)	NS	NS; NS	<i>GJB2</i> <i>SLC26A4</i> <i>MTRNR1</i> <i>MTTL1</i> <i>MTTS1</i>	None	NA
Riedemann[33]	2007	Candidate gene approach	n = 5 (of 50)	MB	NS; German	<i>LRP2</i>	<i>LRP2</i> rs2075252	Unknown
Ross[35]	2009	Pathway approach	n = 33 (of 162)	MB/LGG	European, Indian, East Asian; Canadian	220 drug metabolism genes	<i>TPMT</i> rs12201199 <i>COMT</i> rs9332377	Unknown
Choeyprasert[34]	2012	Candidate gene approach	n = 9 (of 68)	MB/LGG	NS; Thai	<i>GSTT1</i> <i>GSTM1</i> <i>LRP2</i>	<i>GSTT1*1</i> <i>LRP2</i> rs2228171	Enzyme activity ↓ Unknown

Yang[40]	2013	Candidate gene approach	n = 213	MB	NS; American	<i>TPMT</i> <i>COMT</i>	None	NA
Pussegoda[39]	2013	Candidate gene approach	n = 70 (of 317)	NS	Caucasian, other; Canadian	<i>TPMT</i> <i>COMT</i> <i>ABCC3</i> <i>MTHFR</i> <i>VKORC1</i> <i>SLCO1A2</i>	<i>TPMT</i> rs12201199 <i>ABCC3</i> rs1051640	Unknown Unknown
Lanvers-Kaminsky[42]	2014	Candidate gene approach	n = 12 (of 63)	NS	NS; German	<i>TPMT</i> <i>COMT</i>	None	NA
Lanvers-Kaminsky[37]	2015	Candidate gene approach	n = 12 (of 64)	NS	NS; German	<i>SLC22A2</i> <i>SLC31A1</i>	<i>SLC22A</i> rs316019	Substrate affinity
Xu[41]	2015	Genome-wide approach	n = 203 (of 238)	MB	NS; American	1,716,999 variants	<i>ACYP2</i> rs1872328	Unknown
Brown[38]	2015	Candidate gene approach	n = 71	MB	Non-Hispanic white, Hispanic, other; American	<i>SOD2</i>	<i>SOD2</i> rs4880	↑ Oxidative stress in cochlea
Olgun[36]	2016	Candidate gene approach	n = 6 (of 72)	MB	NS; Turkey	<i>ERCC1</i> <i>GSTP1</i> <i>LRP2</i> <i>TPMT</i> <i>COMT</i>	None	None

^a Studies by Peters *et al.*; same cohorts

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; NA, not applicable; NS, not specified.

Table 3: Characteristics of studies of vincristine-induced neurotoxicity in patients with brain tumors

First author [Ref]	Year	Study approach	No. of MB/LGG patients	MB/LGG	Ethnic origin; nationality	Gene(s) investigated	Outcome measures	Associated variant(s)	(Possible) functional role of the genetic variant
Guilhaumou[43]	2011	Candidate gene approach	n = 4 (of 26) ^b	MB/LGG	NS; France	<i>ABCB1</i> <i>CYP3A4</i> <i>CYP3A5</i>	PK parameters	None	NA
Guilhaumou[44]	2011	Candidate gene approach	n = 4 (of 26) ^b	MB/LGG	NS; France	<i>ABCB1</i> <i>CYP3A4</i> <i>CYP3A5</i>	Neurotoxicity events	None	NA
Moore[45]	2011	Candidate gene approach	n = 7 (of 50)	NS	Caucasian, Hispanic, Asian, Pacific Islander, Australian Aboriginal; Australian	<i>CYP3A5</i>	Neurotoxicity	None	NA

^b Studies by Guilhaumou *et al.*; same cohorts

Abbreviations: MB, medulloblastoma; LGG, low-grade glioma; NA, not applicable; NS, not specified; PK, pharmacokinetics.

REFERENCES

1. Ostrom QT, Gittleman H, Farah P *et al.* CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro-oncology* 15 Suppl 2 ii1-56 (2013).
2. Kaatsch P, Rickert CH, Kuhl J, Schuz J, Michaelis J. Population-based epidemiologic data on brain tumors in German children. *Cancer* 92(12), 3155-3164 (2001).
3. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* 17(9), 503-511 (2001).
4. Bandopadhyay P, Bergthold G, London WB *et al.* Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatric blood & cancer* 61(7), 1173-1179 (2014).
5. Gajjar A, Chintagumpala M, Ashley D *et al.* Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *The Lancet. Oncology* 7(10), 813-820 (2006).
6. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro-oncology* 15(1), 97-103 (2013).
7. Gottardo NG, Gajjar A. Current therapy for medulloblastoma. *Current treatment options in neurology* 8(4), 319-334 (2006).
8. Grill J, Sainte-Rose C, Jouvet A *et al.* Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. *The Lancet. Oncology* 6(8), 573-580 (2005).
9. Geyer JR, Sposto R, Jennings M *et al.* Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23(30), 7621-7631 (2005).
10. Reddy AT, Packer RJ. Chemotherapy for low-grade gliomas. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* 15(10), 506-513 (1999).
11. Packer RJ. Childhood medulloblastoma: progress and future challenges. *Brain & development* 21(2), 75-81 (1999).
12. Bull KS, Spoudeas HA, Yadegarfar G, Kennedy CR, Cclg. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 25(27), 4239-4245 (2007).
13. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 19(15), 3470-3476 (2001).
14. Jain P, Gulati S, Seth R, Bakhshi S, Toteja GS, Pandey RM. Vincristine-induced neuropathy in childhood ALL (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. *Journal of child neurology* 29(7), 932-937 (2014).
15. Gregg RB, Wiorek LS, Arvedson JC. Pediatric audiology: a review. *Pediatrics in review* 25(7), 224-234 (2004).
16. Skinner R. Best practice in assessing ototoxicity in children with cancer. *European journal of cancer* 40(16), 2352-2354 (2004).

17. Fouladi M, Chintagumpala M, Ashley D *et al.* Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 26(22), 3749-3755 (2008).
18. Gurney JG, Bass JK, Onar-Thomas A *et al.* Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma. *Neuro-oncology* 16(6), 848-855 (2014).
19. Duval M, Daniel SJ. Meta-analysis of the efficacy of amifostine in the prevention of cisplatin ototoxicity. *Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale* 41(5), 309-315 (2012).
20. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. *European journal of cancer* 40(16), 2445-2451 (2004).
21. Reddel RR, Kefford RF, Grant JM, Coates AS, Fox RM, Tattersall MH. Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. *Cancer treatment reports* 66(1), 19-23 (1982).
22. Rosmarin D, Palles C, Church D *et al.* Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: investigation in the QUASAR2 study, systematic review, and meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 32(10), 1031-1039 (2014).
23. Terrazzino S, Cargnin S, Del Re M, Danesi R, Canonico PL, Genazzani AA. DPYD IVS14+1G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. *Pharmacogenomics* 14(11), 1255-1272 (2013).
24. Meulendijks D, Henricks LM, Sonke GS *et al.* Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *The Lancet. Oncology* 16(16), 1639-1650 (2015).
25. Rocha JC, Cheng C, Liu W *et al.* Pharmacogenetics of outcome in children with acute lymphoblastic leukemia. *Blood* 105(12), 4752-4758 (2005).
26. Diouf B, Crews KR, Lew G *et al.* Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. *Jama* 313(8), 815-823 (2015).
27. Okcu MF, Selvan M, Wang LE *et al.* Glutathione S-transferase polymorphisms and survival in primary malignant glioma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 10(8), 2618-2625 (2004).
28. Barahmani N, Carpentieri S, Li XN *et al.* Glutathione S-transferase M1 and T1 polymorphisms may predict adverse effects after therapy in children with medulloblastoma. *Neuro-oncology* 11(3), 292-300 (2009).
29. Rednam S, Scheurer ME, Adesina A, Lau CC, Okcu MF. Glutathione S-transferase P1 single nucleotide polymorphism predicts permanent ototoxicity in children with medulloblastoma. *Pediatric blood & cancer* 60(4), 593-598 (2013).
30. Peters U, Preisler-Adams S, Hebeisen A *et al.* Glutathione S-transferase genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. *Anti-cancer drugs* 11(8), 639-643 (2000).
31. Peters U, Preisler-Adams S, Lanvers-Kaminsky C, Jurgens H, Lamprecht-Dinnesen A. Sequence variations of mitochondrial DNA and individual sensitivity to the ototoxic effect of cisplatin. *Anticancer research* 23(2b), 1249-1255 (2003).
32. Knoll C, Smith RJ, Shores C, Blatt J. Hearing genes and cisplatin deafness: a pilot study. *The Laryngoscope* 116(1), 72-74 (2006).
33. Riedemann L, Lanvers C, Deuster D *et al.* Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. *The pharmacogenomics journal* 8(1), 23-28 (2008).
34. Choeprasert W, Sawangpanich R, Lertsukprasert K *et al.* Cisplatin-induced ototoxicity in pediatric solid tumors: the role of glutathione S-transferases and megalin genetic polymorphisms. *Journal of pediatric hematology/oncology* 35(4), e138-143 (2013).

35. Ross CJ, Katzov-Eckert H, Dube MP *et al.* Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. *Nature genetics* 41(12), 1345-1349 (2009).
36. Olgun Y, Aktas S, Altun Z *et al.* Analysis of genetic and non genetic risk factors for cisplatin ototoxicity in pediatric patients. *International journal of pediatric otorhinolaryngology* 90 64-69 (2016).
37. Lanvers-Kaminsky C, Sprowl JA, Malath I *et al.* Human OCT2 variant c.808G>T confers protection effect against cisplatin-induced ototoxicity. *Pharmacogenomics* 16(4), 323-332 (2015).
38. Brown AL, Lupo PJ, Okcu MF, Lau CC, Rednam S, Scheurer ME. SOD2 genetic variant associated with treatment-related ototoxicity in cisplatin-treated pediatric medulloblastoma. *Cancer medicine* 4(11), 1679-1686 (2015).
39. Pussegoda K, Ross CJ, Visscher H *et al.* Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clinical pharmacology and therapeutics* 94(2), 243-251 (2013).
40. Yang JJ, Lim JY, Huang J *et al.* The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. *Clinical pharmacology and therapeutics* 94(2), 252-259 (2013).
41. Xu H, Robinson GW, Huang J *et al.* Common variants in ACYP2 influence susceptibility to cisplatin-induced hearing loss. *Nature genetics* 47(3), 263-266 (2015).
42. Lanvers-Kaminsky C, Malath I, Deuster D, Ciarimboli G, Boos J, Am Zehnhoff-Dinnesen AG. Evaluation of pharmacogenetic markers to predict the risk of Cisplatin-induced ototoxicity. *Clinical pharmacology and therapeutics* 96(2), 156-157 (2014).
43. Guilhaumou R, Simon N, Quaranta S *et al.* Population pharmacokinetics and pharmacogenetics of vincristine in paediatric patients treated for solid tumour diseases. *Cancer chemotherapy and pharmacology* 68(5), 1191-1198 (2011).
44. Guilhaumou R, Solas C, Bourgarel-Rey V *et al.* Impact of plasma and intracellular exposure and CYP3A4, CYP3A5, and ABCB1 genetic polymorphisms on vincristine-induced neurotoxicity. *Cancer chemotherapy and pharmacology* 68(6), 1633-1638 (2011).
45. Moore AS, Norris R, Price G *et al.* Vincristine pharmacodynamics and pharmacogenetics in children with cancer: a limited-sampling, population modelling approach. *Journal of paediatrics and child health* 47(12), 875-882 (2011).
46. Hayes JD, Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Critical reviews in biochemistry and molecular biology* 30(6), 445-600 (1995). The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance).
47. Seidegard J, Ekstrom G. The role of human glutathione transferases and epoxide hydrolases in the metabolism of xenobiotics. *Environmental health perspectives* 105 Suppl 4 791-799 (1997).
48. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23(34), 8588-8596 (2005).
49. Bertolini P, Lassalle M, Mercier G *et al.* Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. *Journal of pediatric hematology/oncology* 26(10), 649-655 (2004).
50. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *International journal of radiation oncology, biology, physics* 67(2), 469-479 (2007).
51. Pan CC, Eisbruch A, Lee JS, Snorrason RM, Ten Haken RK, Kileny PR. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. *International journal of radiation oncology, biology, physics* 61(5), 1393-1402 (2005).

52. Van As JW, Van Den Berg H, Van Dalen EC. Medical interventions for the prevention of platinum-induced hearing loss in children with cancer. *The Cochrane database of systematic reviews* doi:10.1002/14651858.CD009219.pub3(7), CD009219 (2014).
53. Oldenburg J, Kraggerud SM, Cvancarova M, Lothe RA, Fossa SD. Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 25(6), 708-714 (2007).
54. Liu H, Pecka JL, Zhang Q, Soukup GA, Beisel KW, He DZ. Characterization of transcriptomes of cochlear inner and outer hair cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 34(33), 11085-11095 (2014).
55. Vos HI, Coenen MJ, Guchelaar HJ, Te Loo DM. The role of pharmacogenetics in the treatment of osteosarcoma. *Drug discovery today* 21(11), 1775-1786 (2016).
56. Hagleitner MM, Coenen MJ, Patino-Garcia A *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* 9(12), e115869 (2014).
57. Renbarger JL, Mccammack KC, Rouse CE, Hall SD. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. *Pediatric blood & cancer* 50(4), 769-771 (2008).
58. Egbelakin A, Ferguson MJ, Macgill EA *et al.* Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. *Pediatric blood & cancer* 56(3), 361-367 (2011).
59. Aplenc R, Glatfelter W, Han P *et al.* CYP3A genotypes and treatment response in paediatric acute lymphoblastic leukaemia. *British journal of haematology* 122(2), 240-244 (2003).
60. Ceppi F, Langlois-Pelletier C, Gagne V *et al.* Polymorphisms of the vincristine pathway and response to treatment in children with childhood acute lymphoblastic leukemia. *Pharmacogenomics* 15(8), 1105-1116 (2014).
61. Stock W, Diouf B, Crews KR *et al.* An Inherited Genetic Variant in CEP72 Promoter Predisposes to Vincristine-Induced Peripheral Neuropathy in Adults With Acute Lymphoblastic Leukemia. *Clinical pharmacology and therapeutics* doi:10.1002/cpt.506 (2016).
62. Gutierrez-Camino A, Martin-Guerrero I, Lopez-Lopez E *et al.* Lack of association of the CEP72 rs924607 TT genotype with vincristine-related peripheral neuropathy during the early phase of pediatric acute lymphoblastic leukemia treatment in a Spanish population. *Pharmacogenetics and genomics* 26(2), 100-102 (2016).
63. Lopez-Lopez E, Gutierrez-Camino A, Bilbao-Aldaiturriaga N, Pombar-Gomez M, Martin-Guerrero I, Garcia-Orad A. Pharmacogenetics of childhood acute lymphoblastic leukemia. *Pharmacogenomics* 15(10), 1383-1398 (2014).
64. Jin TB, Du S, Zhu XK *et al.* Polymorphism in the IL4R gene and clinical features are associated with glioma prognosis: Analyses of case-cohort studies. *Medicine* 95(31), e4231 (2016).
65. Correa DD, Satagopan J, Cheung K *et al.* COMT, BDNF, and DTNBP1 polymorphisms and cognitive functions in patients with brain tumors. *Neuro-oncology* 18(10), 1425-1433 (2016).

ABBREVIATIONS

ABC	ATP-binding cassette
ACYP	Acylphosphatase
ALL	Acute lymphoblastic leukemia
COMT	Catechol-O-methyltransferase
CYP	Cytochrome P450
DPYD	Dihydropyrimidine dehydrogenase
GST	Glutathione S-transferase
GWAS	Genome-wide association study
IL	Interleukin
LGG	Low-grade glioma
LPR	Low-density lipoprotein (Megalin)
MB	Medulloblastoma
NS	Not specified
OR	Odds ratio
OS	Overall survival
PK	Pharmacokinetics
PNET	Primitive neuro-ectodermal tumor
SNP	Single-nucleotide polymorphism
SLC	Solute carrier
SOD	Superoxide dismutase
TPMT	Thiopurine S-methyltransferase

SUPPLEMENTARY

Supplementary table 1: Search strategy for electronic databases

Electronic databases searched	MEDLINE, Embase, Cochrane Library
General search strategy	Keywords and, when available, MeSH-terms were used to draft a search strategy combining the following three elements: "Brain tumor", "Chemotherapy" and "Genetics". Synonyms and related terms were used when appropriate. To broaden the number of articles useful for this systematic review, the first search strategy was combined with a second strategy, consisting the elements "Cisplatin / Carboplatin / Vincristine / Cyclophosphamide / Etoposide / Lomustine", "Genetics" and "Toxicity". By leaving the disease component out of this strategy, studies with heterogeneous cohorts could be identified. These articles were manually screened for presence of brain tumor patients in their cohorts.
Date of search	30 th of October, 2016
Search terms used*:	<p>((("Brain Neoplasms"[Mesh] OR "Medulloblastoma"[Mesh] OR "Glioma"[Mesh] OR "Astrocytoma"[Mesh] OR "Optic Nerve Glioma"[Mesh] OR "Oligodendroglioma"[Mesh] OR "Ganglioglioma"[Mesh] OR brain neoplasm*[Title/Abstract] OR brain cancer[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain tumour*[Title/Abstract] OR medulloblastoma[Title/Abstract] OR glioma[Title/Abstract] OR astrocytoma[Title/Abstract] OR oligodendroglioma[Title/Abstract] OR ganglioglioma[Title/Abstract]) AND ("Drug Therapy"[Mesh] OR drug therapy[Title/Abstract] OR chemotherapy[Title/Abstract] OR "Vincristine"[Mesh] OR vincristine[Title/Abstract] OR "Cisplatin"[Mesh] OR cisplatin[Title/Abstract] OR "Carboplatin"[Mesh] OR carboplatin[Title/Abstract] OR "Cyclophosphamide"[Mesh] OR cyclophosphamide[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract])) OR ((("Cisplatin"[Mesh] OR cisplatin[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR ototoxic*[Title/Abstract] OR hearing loss[Title/Abstract])) OR ((("Carboplatin"[Mesh] OR carboplatin[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR ototoxic*[Title/Abstract] OR hearing loss[Title/Abstract])) OR ((("Vincristine"[Mesh] OR vincristine[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR</p>

"Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR "Polyneuropathies"[Mesh] OR polyneuropathy[Title/Abstract] OR neuropathy[Title/Abstract] OR neurotoxicity[Title/Abstract])) OR (("Cyclophosphamide"[Mesh] OR cyclophosphamide[Title/Abstract]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract] OR "Renal Insufficiency"[Mesh] OR "Kidney Failure, Chronic"[Mesh] OR nephrotoxic*[Title/Abstract] OR renal failure[Title/Abstract] OR kidney failure[Title/Abstract])) OR (("Etoposide"[Mesh] OR etoposide[Title]) AND ("Genomic Structural Variation"[Mesh] OR "Pharmacogenetics"[Mesh] OR "Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh] OR "Genotype"[Mesh] OR "Germ-Line Mutation"[Mesh] OR genetic variant*[Title/Abstract] OR genetic variation*[Title/Abstract] OR gene variation*[Title/Abstract] OR gene variant*[Title/Abstract] OR polymorphism*[Title/Abstract] OR SNP[Title/Abstract] OR pharmacogenetic*[Title/Abstract] OR pharmacogenomic*[Title/Abstract] OR genotype*[Title/Abstract] OR variation*[Title/Abstract] OR variant*[Title/Abstract] OR genetic variability[Title/Abstract] OR germ-line mutation*[Title/Abstract] OR germ-line variation*[Title/Abstract]) AND ("toxicity"[Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR toxicity[Title/Abstract] OR toxicities[Title/Abstract] OR side effect*[Title/Abstract]))))

* The search terms used in MEDLINE are shown; comparable search terms were used for the other electronic databases.