Genetic polymorphisms in candidate genes are not associated with increased vincristine-related peripheral neuropathy in Arab children treated for acute childhood leukemia: a single institution study

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Objective The aim of this study was to evaluate the potential association between candidate genetic polymorphisms and vincristine-related peripheral neuropathy in Arab children with acute lymphoblastic leukemia (ALL).

Patients and methods This is a retrospective evaluation of 133 Arab children treated for ALL at the Children's Cancer Center of Lebanon. Incidence and severity of, as well as the timing (in weeks) at which grade 2 or higher peripheral neuropathy occurred were recorded. Genotyping for *ABCB1* (*rs1045642*), *ABCB1* (*rs1128503*), *ABCC2* (*rs717620*), *CEP72* (*rs924607*), *ETAA1* (*rs17032980*), and *MTNR1B* (*rs12786200*) was performed.

Results A total of 26 (19.5%) individuals developed peripheral neuropathy, three of which occurred during the induction phase. No statistically significant associations were revealed for any of the polymorphisms with either incidence of vincristine-related toxicity, toxicity severity, or time to the first episode of grade 2 or higher vincristine-related peripheral neuropathy.

Conclusion This study presents the first pharmacogenetic analysis of vincristine-related peripheral neuropathy in children with ALL in an Arab country. We have shown that genetic polymorphisms in candidate genes are not associated with peripheral neuropathy secondary to chronic therapy with high-dose vincristine (2 mg/m^2) during the continuation phase. Concerning *CEP72*, our results are in line with the findings from the St Jude cohort of children treated for ALL with higher vincristine doses during chronic treatment. Larger high-throughput genetic analyses may be warranted to evaluate variants in other candidate genes such as *CYP3A5* and reveal new nonpreviously reported alleles that may be peculiar to this region of the world. *Pharmacogenetics and Genomics* 28:189–195 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

The introduction of novel therapeutic approaches and dedicated treatment protocols for children with acute lymphoblastic leukemia (ALL) surely translated into improved outcomes, such as survival rates exceeding 90% in most developed countries [1]. However, there remain continuous efforts to optimize safety of treatment because, although the doses for antileukemic agents are calculated according to standardized protocols, prediction of toxicity is still difficult owing to wide interindividual variability. Based on this, investigators have been extensively assessing associations between candidate gene polymorphisms and ALL treatment toxicity and outcome. The focus has been on the commonly used drugs with the most compelling evidence being for 6-mercaptopurine therapy and risk of myelosuppression [2–4]. We have recently used the candidate gene approach and shown clinically significant results with methotrexate and 6-mercaptopurine-related myelotoxicity [5,6]; nevertheless, we noticed additional adverse events that are worth pursuing. These include somatic, sensory, and motor peripheral neuropathies that are peculiar and dose limiting to vincristine therapy [7]. As a matter of fact, the vinca alkaloids' pharmacokinetics were previously shown to be associated with a large interindividual variability [8,9]. In addition, Renbarger *et al.* [10] have reported significant differences in neuropathy

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toxicity grades between White and African Americans, suggesting a role for genetics in vincristine-related interindividual variability.

The main candidate genes studied in childhood ALL in relation to vincristine pharmacokinetics (PK) are the drug-metabolizing enzyme cytochrome P450 (CYP) 3A5 and the ATP-binding cassette (ABC) drug transporters such as ABCB1 and ABCC2 that play a major role in biliary excretion of vincristine [10–14]. To our knowledge, few reports have evaluated the clinical effects of common single nucleotide variants (SNVs) in these candidate genes in pediatric patients with ALL treated with vincristine; nevertheless, data are inconsistent and sometimes inconclusive [15–20].

Owing to the realization that predisposition to drug toxicity is a complex and polygenic process, candidate gene approaches have been challenged with advocacy for technologies that do not require a priori gene and/or SNV identification. Recently, in a genome-wide association study, SNVs in *CEP72*, *ETAA1*, and *MTNR1B* genes (among others) were reported to be associated with vincristine-related neuropathy in two independent cohorts of patients treated with the St Jude Total XIII and the Children's Oncology Group AALL0433 protocols [21].

In this study, we aimed to evaluate the association between *ABCB1*, *ABCC2*, *CEP72*, *ETAA1*, and *MTNR1B* candidate SNVs and vincristine-related peripheral neuropathy in our cohort of Arab patients treated for ALL at the Children's Cancer Center of Lebanon.

Patients and methods

Patients and data collection

This study was approved by the American University of Beirut Institutional Review Board and builds on a previously described retrospective cohort that included children consecutively diagnosed and treated for ALL at the Children's Cancer Center of Lebanon between 2010 and 2013 [5,6]. Whole blood samples were collected, and medical charts were reviewed for baseline demographics and treatment-related data. A total of 143 patients were originally recruited, of whom 133 were initiated and maintained on our treatment protocol and were hence evaluated.

Our treatment protocol is adopted from the St Jude Children's Research Hospital Total XV therapy with minor modifications. The protocol consists of three phases of therapy: induction for 6 weeks, consolidation for 8 weeks, and continuation for 146 weeks for males and 120 weeks for females. Two more intensive phases of therapy are given during weeks 7–9 (re-induction 1) and 17–19 (re-induction 2) of continuation treatment. The consolidation phase consists of high-dose methotrexate every other week in addition to daily 6-mercaptopurine but does not include vincristine therapy. Vincristine is given as an intravenous injection during the induction and continuation phases of the treatment protocol: 1.5 mg/m^2/week for four doses during induction, and 2.0 mg/m^2 every 4 weeks during continuation up to week 100. The two re-induction cycles entail 3 weekly doses of vincristine (1.5 mg/m^2).

Patients are assigned to either of two protocol arms, low risk or intermediate/high risk, based on disease risk. The major difference between both protocol arms is the dose of high-dose methotrexate during consolidation phase and the inclusion of 12 cycles of low-dose cyclophosphamide and cytarabine during continuation therapy. There are no differences in vincristine administration schedule and doses between both protocol arms [22]. Of note is that administration of azole antifungals is avoided during vincristine therapy.

Retrospective review of clinical history and physical examination sections of the medical charts was performed for identification of vincristine-related peripheral neuropathy. Signs and symptoms reviewed included upper and/or lower extremities' tingling or numbness, jaw pain, hoarseness, constipation, neuropathic pain, and decreased strength in the peripheral parts of the upper and/or lower extremities. Incidence of peripheral neuropathy was categorized as yes/no, and its highest severity (as applicable) was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) [23]. The scale classifies vincristine-related neuropathy into the following: mild (grade 1), moderate (grade 2), severe (grade 3) and life-threatening (grade 4). For the current analysis, we only identified patients with greater than grade 1 toxicity. Furthermore, vincristine cumulative dose (mg/m^2) and the time (in weeks) at which the first episode of grade 2 and higher peripheral neuropathy occurred were recorded. For individuals who did not develop grade 2 or higher peripheral neuropathy, the cumulative dose and week during which the last vincristine dose was administered were recorded.

Genotyping

DNA was extracted from peripheral whole blood using a Qiagen (Germantown, Maryland, USA) DNA isolation kit according to guidelines and stored at -20°C until analysis. Genotyping for *CEP72* (*rs924607*), *ETAA1* (*rs17032980*), and *MTNR1B* (*rs12786200*) SNVs was performed using TaqMan (Thermo Fisher Scientific, Waltham, Massachusetts, USA) allele discrimination assays on a CFX384 real-time PCR from Bio-Rad (Hercules, California, USA). *ABCB1 C3435T* (*rs1045642*), *ABCB1 C1236T* (*rs1128503*), and *ABCC2 −24C>T* (*rs717620*) genotyping was previously performed using light SNP (Roche, Basel, Switzerland) assays on a Roche Lightcycler (Basel, Switzerland) [5]. Overall, 10% of samples were genotyped twice, and results showed 100% reproducibility.

The *CEP72*, *ETAA1*, and *MTNR1B* variants were chosen with the aim to potentially replicate the top significant variants from the genome-wide association study results of Diouf *et al.* [21] in an Arab cohort. Genotyping results of the *ABCC2* and *ABCB1* variants were already available to us when we evaluated them as candidate SNVs for the pharmacogenetics of methotrexate [5]. We included them in the current analysis as both genes are involved in the PK of vincristine [20].

Statistical analysis

Data were entered and analyzed using SPSS version 24.0 (IBM, Armonk, New York, USA). A two-sided P value of less than 0.05 was considered statistically significant.

Genotype frequencies were computed and tested for Hardy–Weinberg equilibrium using χ^2-test. Genetic analysis was performed in three ways: comparing homozygous variant alleles to heterozygous and wild-type homozygous, using the recessive allele model that compares wild-type genotypes with variant allele carriers, and comparing homozygous variant alleles to the combination of heterozygous with wild-type homozygous. The latter was performed with the relatively common variants only.

The associations between baseline demographics (age, sex, and protocol arm), vincristine cumulative dose, and genotype groups with incidence and grade of vincristine-related peripheral neuropathy were analyzed using Fisher exact test or nonparametric Mann–Whitney U or Kruskal–Wallis test as appropriate. Univariate binomial logistic regression was also performed to evaluate the risk of vincristine-related peripheral neuropathy with the different genotype groups. This was coupled with a multivariate logistic regression with vincristine cumulative dose as a covariate. To assess for the association between the different genotypes and time to failure being the time to the first episode of grade 2 or higher vincristine neuropathy, survival analyses were carried out using Kaplan–Meier curves. Statistical significance was assessed using the log-rank test. Multivariate Cox-proportional hazard analyses were also carried out to adjust for vincristine cumulative dose as a potentially confounding covariate.

Results

Sample characteristics

The sample included 133 children, with mean ± SD age of 6.71 ± 5.01 years, comprising 76 (57.1%) males and 57 (42.9%) females. All were white. Overall, 15 were non-Lebanese: seven Palestinians, five Syrians, and three Iraqis. Of the 133 children, 66 (50.4%) were allocated to the low-risk treatment protocol arm, whereas 65 (49.6%) were allocated to the intermediate-risk/high-risk arm. All patients had finished treatment at the time of analysis, hence complete follow-up is available. No patient was taking any potent CYP3A4 inhibitors such as azole antifungals for at least 48 h before and until at least 48 h after each vincristine dose, and none had disease such as Charcot–Marie–Tooth that would increase susceptibility to neuropathy.

Vincristine-related peripheral neuropathy

A total of 26 (19.5%) children developed signs and symptoms of peripheral neuropathy, of which 21 (15.8%) were moderate (grade 2) and 5 (3.7%) were severe (grade 3). None of the patients developed life-threatening neuropathy (grade 4). Only three patients had the first grade 2 or above neuropathic episode during the induction phase: one at week 2 and two at week 4; hence the rate of vincristine-related peripheral neuropathy being 2.25 and 17.29% during induction and continuation phases, respectively. Knowing from previous literature that the *CEP72* variant – being the most compelling – was not shown to play a significant role in vincristine-related peripheral neuropathy during the induction phase of ALL therapy [24,25], and in order not to dilute the toxicity incidence during the continuation phase with the less common incidence during induction, we excluded the three patients who developed peripheral neuropathy during induction in the analysis that follows ($N = 130$). None of these individuals was homozygous for any of the evaluated variants.

Genetic polymorphisms

Table 1 shows the frequency distribution of the six evaluated SNVs. As expected, the calculated minor allele frequencies were comparable to reported Global and HapMap-CEU minor allele frequencies. All SNVs were in Hardy–Weinberg equilibrium except for *ETAA1* (*rs17032980*), probably owing to chance or the small sample size, as there was no evidence of genotyping errors; it was hence excluded from further analysis. As expected, *ABCB1 rs1045642* and *rs1128503* SNVs were in linkage disequilibrium, with a Pearson correlation of 0.725 ($P < 0.001$).

Associations with vincristine-related peripheral neuropathy

As shown in Table 2, no statistically significant differences were seen by age, sex and protocol arm. Although vincristine-related neuropathy is expected to occur at higher cumulative vincristine doses [26], we expected to find significantly lower cumulative doses at grade 2 and above peripheral neuropathy in our results owing to the fact that, in this category, the cumulative dose is a partial sum of the doses, whereas for those who did not develop grade 2 and above peripheral neuropathy, it is the total across the entire therapy.

No statistically significant associations were revealed with incidence of vincristine-related toxicity, toxicity severity, and time to the first episode of grade 2 or higher vincristine-related peripheral neuropathy for any of the five SNVs when comparing homozygous variant alleles to heterozygous and wild-type homozygous alone (Table 2 and Fig. 1). Similarly, no significant results were shown when combining genotypes (Supplementary Tables 1 and 2, Supplemental digital content 1, *http://links.lww.com/FPC/B317*). In addition, multivariate

Table 1 Frequency distribution of the evaluated single nucleotide variants

Genes	SNV	Homozygous wild type [*n* (%)]		Heterozygous [*n* (%)]		Homozygous variant allele [*n* (%)]		HWE *P* value[a]	Sample MAF	Global MAF[b]	HapMap-CEU MAF[c]
CEP72	*rs924607*	CC	56 (43.1)	CT	52 (40.0)	TT	22 (16.9)	0.11	0.37	0.28	0.39
ETAA1	*rs17032980*	AA	80 (61.5)	AG	37 (28.5)	GG	13 (10.0)	0.01	0.24	0.27	0.23
MTNR1B	*rs12786200*	CC	84 (64.6)	CT	45 (34.6)	TT	1 (0.8)	0.05	0.18	0.23	0.22
ABCC2	*rs717620*	CC	102 (78.5)	CT	25 (19.2)	TT	3 (2.3)	0.34	0.12	0.13	0.18
ABCB1	*rs1045642*	CC	37 (28.5)	CT	58 (44.6)	TT	35 (26.9)	0.22	0.49	0.39	0.43
	rs1128503	CC	43 (33.1)	CT	60 (46.2)	TT	27 (20.8)	0.47	0.44	0.41	0.45

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; SNV, single nucleotide variant.
[a]*P*-values were computed by χ^2-test.
[b]Global MAF (*https://www.ncbi.nlm.nih.gov/projects/SNP/docs/rs_attributes.html#gmaf*).
[c]HapMap-CEU (*https://www.ncbi.nlm.nih.gov/projects/SNP/snp_viewTable.cgi?pop=1409*).

Table 2 Associations of baseline characteristics and genetic polymorphisms with incidence and grade of vincristine-related peripheral neuropathy

	Vincristine-related grade 2 and above peripheral neuropathy			Grade of vincristine-related peripheral neuropathy		
	No	Yes	*P* value[b]	Grade 2	Grade 3	*P* value[b]
Age (mean ± SD) (years)	6.45 ± 5.02	7.09 ± 4.38	0.313	6.47 ± 4.45	10.00 ± 2.83	0.186
Sex [*n* (%)]						
Males	61 (57.0)	13 (56.5)	0.572	11 (57.9)	2 (50.0)	0.501
Females	46 (43.0)	10 (43.5)		8 (42.1)	2 (50.0)	
Protocol arm [*n* (%)]						
Low	51 (48.6)	14 (60.9)	0.201	12 (63.2)	2 (50.0)	0.198
Intermediate/high	54 (51.4)	9 (39.1)		7 (36.8)	2 (50.0)	
Vincristine cumulative dose[a] (mean ± SD) (mg/m^2)	65.99 ± 6.11	27.91 ± 12.09	< 0.001	29.47 ± 12.59	20.50 ± 5.74	< 0.001
CEP72 (*rs924607*) [*n* (%)]						
CC	47 (43.9)	9 (39.1)		6 (31.6)	3 (75.0)	
CT	42 (39.3)	10 (43.5)		9 (47.4)	1 (25.0)	
TT	18 (13.8)	4 (3.1)	0.953	4 (21.1)	0 (0.0)	0.519
MTNR1B1 (*rs12786200*) [*n* (%)]						
CC	67 (62.6)	17 (73.9)	0.563	15 (78.9)	2 (50.0)	0.231
CT	39 (36.4)	6 (26.1)		4 (21.1)	2 (50.0)	
TT	1 (30.0)	0 (0.0)		0 (0.0)	0 (0.0)	
ABCC2 (*rs717620*) [*n* (%)]						
CC	84 (78.5)	18 (78.3)	0.876	14 (73.7)	4 (100.0)	0.403
CT	20 (18.7)	5 (21.7)		5 (26.3)	0 (0.0)	
TT	3 (2.8)	0 (0.0)		0 (0.0)	0 (0.0)	
ABCB1 (*rs1045642*) [*n* (%)]						
CC	31 (29.0)	6 (26.1)	0.957	6 (31.6)	0 (0.0)	0.326
CT	47 (43.9)	11 (47.8)		10 (52.6)	1 (25.0)	
TT	29 (27.1)	6 (26.1)		3 (15.8)	3 (75.0)	
ABCB1 (*rs1128503*) [*n* (%)]						
CC	35 (32.7)	8 (34.8)	0.693	8 (42.1)	0 (0.0)	0.351
CT	51 (47.7)	9 (39.1)		6 (31.6)	3 (75.0)	
TT	21 (19.6)	6 (36.1)		5 (26.3)	1 (25.0)	

[a]Although vincristine-related neuropathy is expected to occur at higher cumulative vincristine doses, the significantly lower cumulative dose at grade 2 and above peripheral neuropathy is owing to the fact that, in this category, the cumulative dose is a partial sum of the doses, whereas for those who did not develop grade 2 and above peripheral neuropathy, it is the total across the entire therapy. This is because we had complete follow-up on all patients.
[b]*P* values were computed by Fisher exact test or nonparametric Mann–Whitney *U* or Kruskal–Wallis tests as appropriate.

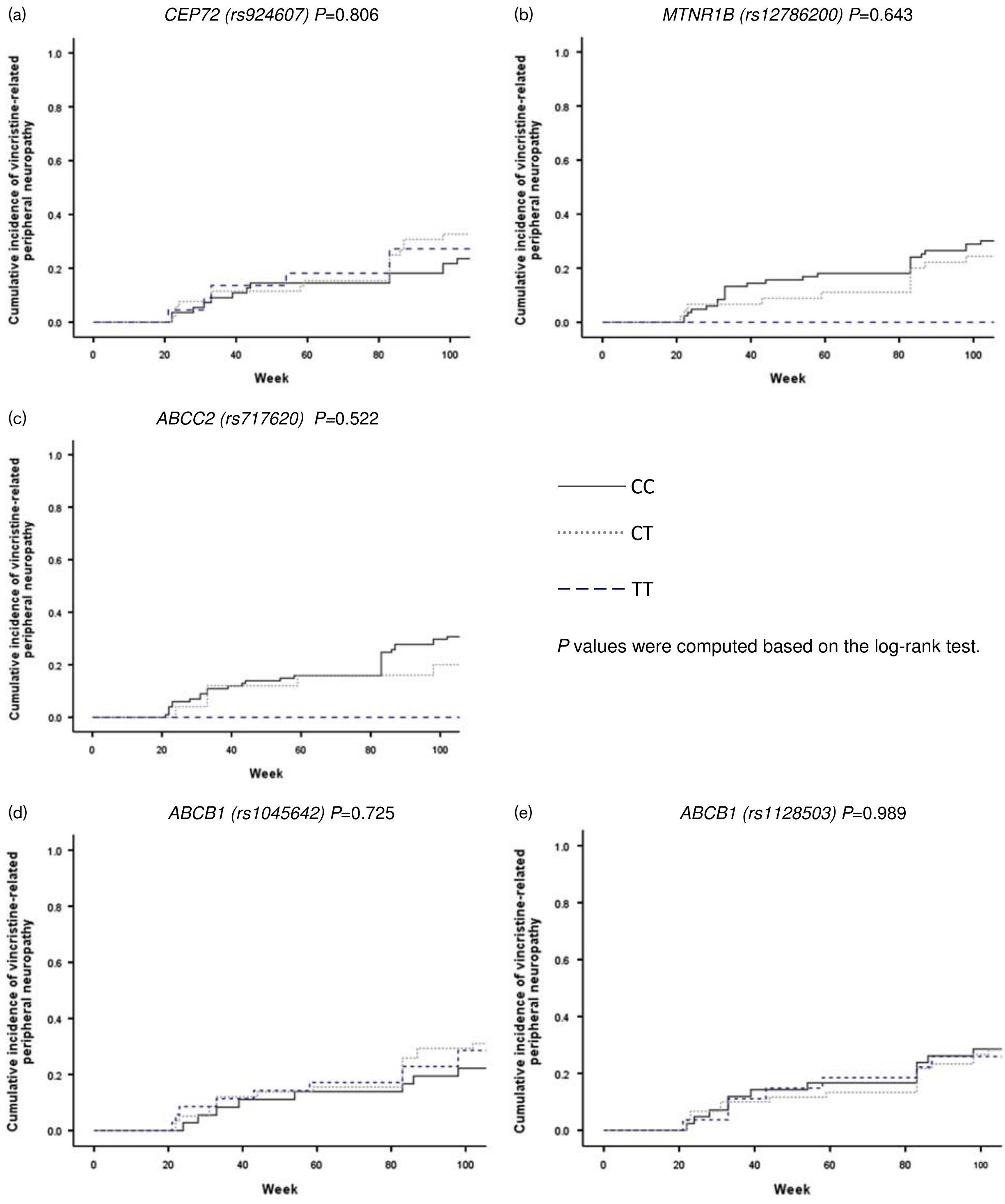
binomial logistic regression (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/FPC/B317*) and cox regression analyses (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/FPC/B317*) with vincristine cumulative dose as a covariate did not reveal any significant results either.

Discussion

This study presents the first pharmacogenetic analysis of vincristine-related peripheral neuropathy in children with ALL in an Arab country. We have shown that genetic polymorphisms in candidate genes are not associated with peripheral neuropathy secondary to chronic therapy with high-dose vincristine (2 mg/m^2) during the continuation phase.

Concerning *ABCB1* (*rs1045642*), this SNV is relatively common and known to be associated with decreased protein function [27]. Accordingly, it is expected that *ABCB1* (*rs1045642*) variant allele carriers have a lesser ability to export vincristine out of the hepatocyte into the bile, which is translated into higher plasma concentrations of vincristine and hence higher toxicity. Despite this plausible hypothesis, the literature concerning *ABCB1* in relation to vincristine-related peripheral

Fig. 1



Cumulative incidence of grade 2 and above vincristine-related peripheral neuropathy by (a) CEP72 (rs924607), (b) MTNR1B (rs12786200), (c) ABCC2 (rs717620), (d) ABCB1 (rs1045642) and (e) ABCB1 (rs1128503) genotype.

neuropathy has been non-conclusive, probably owing to non-standardized toxicity measurement, relatively small sample sizes, and complexity of treatment protocols. Plasschaert *et al.* [15] genotyped 52 Dutch children with ALL for the *ABCB1 C3435T* (*rs1045642*) and *G2677T* (*rs2032582*) SNVs and showed no association with vincristine PK parameters and constipation. Similarly, Hartman *et al.* [16] genotyped 36 additional Dutch children with ALL for these same *ABCB1* SNVs and for *CYP3A5*3* SNV, which is associated with decreased expression of *CYP3A5*, and also showed no effect of these polymorphisms on motor performance. More recently, Ceppi *et al.* [18] investigated peripheral neuropathy and outcome in more than 300 Canadian patients with ALL by genotyping for 17 polymorphisms in six genes of interest including *ABCB1* and showed that the polymorphisms in the two target genes *ACTG1* and *CAPG* as well as *ABCB1* may modulate vincristine-related peripheral neuropathy. For instance, substitution in the promoter of the *ABCB1* gene (*rs4728709*) had a protective effect against lower grade peripheral neuropathy. In addition, C–A variation located 17 nucleotides upstream from the transcription start site (*rs3770102*) had a protective effect against high-grade peripheral neuropathy. As for the *ABCB1* (*rs1045642*) SNV, patients with the *3435TT* genotype had lower event-free survival; yet this association was not replicated in the set of 275 patients from the Dana-Farber Cancer Institute [18] and in another, though much smaller and less recent, subset of patients with ALL [19].

Concerning the *CEP72*, *ETAA1*, and *MTNR1B* candidate SNVs, probably the most surprising result was that we found no association of vincristine-related neuropathy with the *CEP72* (*rs924607*) SNV. This is despite the compelling in-vivo and in-vitro evidence supporting its role in lowering the expression of the *CEP72* gene, which is responsible for the production of a protein that is important for microtubule formation, hence increasing the cell's sensitivity to vincristine [21]. Nevertheless, our results are in line with the findings from the St Jude cohort of children treated for ALL with higher vincristine doses ($2\,mg/m^2$) during continuation treatment [21]. Although it is not very clear why the significant role of this variant has only been shown with chronic treatment with lower doses ($1.5\,mg/m^2$) of vincristine, it has been postulated that higher vincristine doses are toxic enough and hence may not require the additional enhanced sensitivity caused by the polymorphism [25]. It is also possible that our sample size is not adequately powered to detect statistical significance, especially that our rate of vincristine-related peripheral neuropathy was lower than that reported in the continuation phase of the St Jude (64/222 = 28.8%) and Children's Oncology Group (22/99 = 22.2%) cohorts [21], though we had the same frequency of the *CEP72 TT* genotype (16%). The positive results reported by Stock *et al.* [28] were based on three independent treatment cohorts of a total of 783 participants including adults, of which 48 eligible cases of grade 2 and above vincristine-related neurotoxicity and 48 matched controls were extracted. Our study is also limited by being based on retrospective chart review with potentially missing documentation of vincristine-related peripheral neuropathy. Furthermore, our 'negative results' can be explained by the potential diversity in pharmacogenetic associations in different populations [25]. Interestingly, there was also a lack of association of this SNV with vincristine-related peripheral neuropathy in 142 Spanish children with ALL [24]. In this study, however, although the rate of vincristine-related neuropathy was relatively high (25.4%), the *CEP72 TT* genotype was less common (11.3%). In addition, the analysis was limited to the early phase of treatment, and the authors argued that their results are hence not comparable to the US data. In our case, most cases (all but 3) of vincristine-related peripheral neuropathy occurred at the continuation (later) phase of treatment. In the same Spanish cohort, the authors postulated that neurotoxicity may be more related to genes involved in the metabolism and transport of vincristine, and as a matter of fact, they observed strong associations with two *ABCC2* SNVs from a total of 150 candidates. These *ABCC2* SNVs were, however, different from the one we analyzed [20].

Conclusion

This study presents the first pharmacogenetic analysis of vincristine-related peripheral neuropathy in children with ALL in Arabs. Further studies with larger sample sizes are needed to ascertain our results. Larger throughput genetic analyses may also be warranted to evaluate variants in other candidate genes such as *CYP3A5* and reveal new nonpreviously reported alleles that are peculiar to this region of the world [25].

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Conflicts of interest

There are no conflicts of interest.

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