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# Association between *CEP72* genotype and persistent neuropathy in survivors of childhood acute lymphoblastic leukemia

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Five-year survival rates for childhood acute lymphoblastic leukemia exceed 90% (1). However, acute treatment-related adverse events are common, and are not always transient. Over 40% of long-term ALL survivors report sensory and/or motor neuropathy symptoms that interfere with movement (2) and quality of life (3). Identifying risk factors for persistent neuropathy is needed to target survivors who will benefit from preventive or restorative interventions. Recent data indicate that a single nucleotide polymorphism (rs924607) in the promoter region of the *CEP72* gene is associated with incidence and severity of acute peripheral neuropathy (4, 5), where those homozygous for the rs924607 risk allele (TT) are at greatest risk for acute neuropathy (4). It is unknown whether this variant predisposes to persistent neuropathy. Thus, the purpose of this study was to determine associations between the *CEP72* genotype (rs924607) and prevalence and severity of persistent motor and sensory neuropathy in childhood ALL survivors ≥5 years from diagnosis.

Participants were enrolled in the Institutional Review Board approved St. Jude Lifetime Cohort Study (NCT00760656) (6), treated at St Jude Children's Research Hospital 1962–



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Author Contributions

CGG contributed to data collection, analyzed and interpreted data, wrote and revised the manuscript. BD and WY contributed to conceptualizing the study, interpreted data and reviewed the manuscript. YS contributed to data collection, provided analysis support, and reviewed the manuscript. ERF contributed to data interpretation and manuscript review. REP and MDW contributed to data collection and manuscript review. MMH, ZW, and SJ supervised data collection, interpreted data and reviewed the manuscript. LLR provided administrative and material support, interpreted data, and reviewed the manuscript. WEE conceptualized and designed the study, interpreted data, and reviewed the manuscript. KKN conceptualized and designed the study, supervised data collection, analyzed and interpreted data, wrote and revised manuscript.

Competing Interests Statement

The authors declare no competing financial interests in relation to the work described.

2012, and ≥5 years post diagnosis. Participants completed questionnaires, medical and physical assessments and provided biospecimens for genetic studies. Medical records were abstracted for treatment exposures and significant health events (including acute neuropathy) (Supplemental Methods). Survivors eligible for these analyses had a primary diagnosis of ALL and no history of peripheral vascular disease, diabetes, or non-digit amputation. Of 1361 potentially eligible participants, 253 (18.6%) were excluded because existing conditions precluded accurate neuropathy ascertainment or germline DNA was unavailable (received hematopoietic stem cell transplant). An additional 118 (10.6%) had missing genomic or assessment data, resulting in a final sample size of 990 (Figure S1).

Persistent neuropathy was defined as a National Cancer Institute Common Terminology for Adverse Events, version 5, grade ≥2 motor or sensory neuropathy (7) (Table S1). Grade assignment used data from the modified Total Neuropathy Scale (mTNS)(8, 9) and performance on functional measures. mTNS scores range from 0-24 for adults and 0-32 for children (higher is worse). The pediatric version was rescaled to a 24-point maximum. Performance measures included hand grip and ankle dorsiflexion strength for all participants, balance and fine motor function for adults, and self-reported tripping, inability to climb stairs or inability to button or zip clothing for children (Supplemental Methods). Those with motor signs/symptoms were categorized with grade 1 (mild), those with motor signs/symptoms and impaired strength ($<10^{th}$ percentile of age and sex predicted) in either the hands/ankles with grade 2 (moderate), and those with motor signs/symptoms and impaired strength in both hands/ankles with grade 3 (severe/disabling) motor neuropathy. Those with sensory signs/symptoms were categorized with grade 1, those with sensory signs/symptoms and impaired balance (composite score on the sensory organization test <70) or fine motor skills (≥10 seconds to write “Whales live in the blue ocean”) with grade 2, and those with sensory signs/symptoms, impaired balance and fine motor skills with grade 3 sensory neuropathy. Among children, those with sensory signs/symptoms were categorized with grade 1, those with sensory signs/symptoms, and who reported tripping while walking, difficultly climbing stairs or difficulty buttoning or zipping clothing with grade 2, and those with sensory signs/symptoms, and who reported at least two of tripping while walking, difficulty climbing stairs or difficulty buttoning or zipping clothing with grade 3 sensory neuropathy.(9)

*CEP72* genotypes (rs924607) were determined by whole-genome sequencing (WGS) or Affymetrix® Genome-Wide Human Single Nucleotide Polymorphism (SNP) Array 6.0 (Affymetrix SNP6.0; Affymetrix Incorporated, Santa Clara, CA, USA) (Supplemental Methods).

Multivariable logistic and linear regression were used to evaluate associations between *CEP72* genotype and persistent neuropathy or mTNS score adjusted for clinical risk factors including sex, age at diagnosis, age at neuropathy assessment, genetic ancestry, cranial radiation exposure, and cumulative vincristine dose (or history of acute neuropathy) (Supplemental Methods). Analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Participants and non-participant characteristics are shown in Table S2. The proportion of CEP72 genotypes for participants were 44.6% CT, 42.4% CC, and 13.0% TT. Persistent neuropathy was present in 16.0% of survivors, 12.5% with sensory, 7.2% with motor, and 3.7% with both motor and sensory neuropathy. The prevalence of motor neuropathy was higher in individuals with at least one risk 'T' allele at rs924607 (TT genotype 10.9%, CT genotype 8.6%,) compared to those without the risk allele (CC genotype, 4.5%) (Fig 1 and Table S3). After accounting for clinical risk factors (Fig 2 and Table S4) , risk for motor neuropathy was highest among individuals with TT (OR 2.47; 95% CI 1.15–5.31), followed by CT (OR 1.93; 96% CI 1.06–3.51), compared to CC genotypes. Similarly, CT genotypes were associated with higher total (β=0.48; 95% CI 0.15–0.82) and motor subscale scores (β=0.33; 95% CI 0.10–0.57) on the mTNS, indicating risk for more severe symptoms (Table S5). The inclusion of acute neuropathy history in multivariate models, or exclusion of survivors with cranial radiation, did not change associations between genotype and persistent neuropathy risk or severity (Tables S6-S10).

In this study, persistent neuropathy was prevalent in 16% of long-term childhood ALL survivors. Consistent with reports of *acute* peripheral neuropathy among children and adults during treatment for ALL, our study indicates host genetics ('T' risk allele in *CEP72*) are associated with prevalence and severity of *persistent* motor neuropathy, characterized not only by symptoms, but also by significant distal muscle weakness.

The prevalence of persistent neuropathy in our study population is somewhat lower than reported by others,(10-12) likely because we defined persistent neuropathy as a combination of signs/symptoms and functional loss. Previous research has focused primarily on signs/symptoms to define neuropathy. Our approach allowed for the identification of survivors whose neuropathy results in, or who are risk for functional loss, and who might most benefit from rehabilitation (2).

Our identification of an association between *CEP72* 'T' allele and persistent motor neuropathy is consistent with our identification of this variant in children with ALL who develop acute neuropathy during vincristine therapy, and whose leukemia cells are more sensitive to vincristine *ex vivo* (4). The *CEP72* 'T' allele is also a risk factor for neuropathy among adult patients with ALL during treatment (5). *CEP72* encodes a centrosomal protein 72kDa essential for microtubule formation and organization. Variation in rs924607 in the promoter region creates a binding site for a transcriptional repressor that can reduce centrosomal protein translation, potentially compromising microtubule organization and stability, and thus axonal integrity (4, 13).

We found an association between expression of the 'T' risk allele and persistent motor, but not sensory, neuropathy. Although the biological mechanism for this difference is not clear (motor and sensory nerves rely on microtubule organization for efficient axonal transport), a recent meta-analysis describing associations between CEP72 allelic variations and neuropathy indicates the association is present when the phenotype is precise and includes a loss of function (14). Thus, while our data supports use of genetic screening to identify children most likely to experience persistent motor neuropathy during survivorship,

future mechanistic studies to better understand the differential impact of vincristine on motor and sensory neurons in long-term survivors are needed.

Severity of acute neuropathic symptoms is dose related, often requiring withdrawal of causative agents, potentially compromising treatment efficacy and survival. Thus, identifying children at genetic risk early is important so that interventions or appropriate treatment modifications can be initiated. Although several randomized clinical trials have assessed therapeutic interventions to remediate acute peripheral neuropathy during vincristine administration, including adjuvant pharmacotherapy and exercise (Table S11), current guidelines suggest only dose-reduction and delay strategies to manage neuropathy (15). Fortunately, an ongoing randomized clinical trial (NCT03117751) uses genetic data to inform treatment to improve survival and limit treatment-related side effects for children newly diagnosed with ALL.

Results should be considered in the context of limitations. First, analyses were cross-sectional; persistent neuropathy may have been present since treatment or emerged during survivorship. In addition, identification of acute neuropathy depended upon medical record documentation of signs/symptoms during treatment 1962-2012; detail was likely inconsistent. Additionally, analyses were not adjusted for antifungal therapy or liver or kidney dysfunction during ALL therapy, did not include survivors who died prior to study initiation, and included survivors treated at a single institution, perhaps biasing our estimates and limiting generalizability. Finally, we did not use electrophysiologic methods in this study, an approach able to detect subclinical impairment even in the absence of clinical sensory signs.

In summary, our findings indicate that risk for persistent motor neuropathy is independently associated with *CEP72* genotype. Given that children with ALL with homozygous ‘TT’ genotypes have leukemic cells more sensitive to vincristine (4), our data support the need to test interventions that employ vincristine dose reduction among children genetically predisposed to develop neuropathy. This is important to the growing childhood cancer survivor population as peripheral neuropathy in long-term survivors is associated with poor mobility and reduced walking endurance (2). Genetic screening of children with, and survivors of, childhood ALL may identify individuals at greatest risk for persistent neuropathy, and inform strategies, including targeted rehabilitation, to prevent development of impairments later in life.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## REFERENCES


1. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, et al. Improved CNS control of childhood acute llymphoblastic leukemia without cranial irradiation: St. Jude Total Therapy Study 16. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2019; 37: 3377–3391. [PubMed: 31657981]
2. Varedi M, Lu L, Howell CR, Partin RE, Hudson MM, Pui CH, et al. Peripheral neuropathy, sensory processing, and balance in survivors of acute lymphoblastic leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018; 36: 2315–2322. [PubMed: 29812998]
3. Huang IC, Brinkman TM, Kenzik K, Gurney JG, Ness KK, Lanctot J, et al. Association between the prevalence of symptoms and health-related quality of life in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013; 31: 4242–4251. [PubMed: 24127449]
4. Diouf B, Crews KR, Lew G, Pei D, Cheng C, Bao J, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. Jama 2015; 313: 815–823. [PubMed: 25710658]
5. Stock W, Diouf B, Crews KR, Pei D, Cheng C, Laumann K, 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 2017; 101: 391–395. [PubMed: 27618250]
6. Howell CR, Bjornard KL, Ness KK, Alberts N, Armstrong GT, Bhakta N, et al. Cohort Profile: The St. Jude Lifetime Cohort Study (SJLIFE) for paediatric cancer survivors. Int J Epidemiol 2021; 50: 39–49. [PubMed: 33374007]
7. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. The New England journal of medicine 2006; 355: 1572–1582. [PubMed: 17035650]
8. Wampler MA, Miaskowski C, Hamel K. The modified Total Neuropathy Score: A clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer. J Support Oncol 2006; 4: 9–16.
9. Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: A reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. Support Care Cancer 2013; 21: 847–856. [PubMed: 22993026]
10. 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 2014; 29: 932–937. [PubMed: 23781018]
11. Ramchandren S, Leonard M, Mody RJ, Donohue JE, Moyer J, Hutchinson R, et al. Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. J Peripher Nerv Syst 2009; 14: 184–189. [PubMed: 19909482]
12. Tay CG, Lee VWM, Ong LC, Goh KJ, Ariffin H, Fong CY. Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukaemia. Pediatr Blood Cancer 2017; 64: e26471.
13. Almeida-Souza L, Timmerman V, Janssens S. Microtubule dynamics in the peripheral nervous system: A matter of balance. Bioarchitecture 2011; 1: 267–270. [PubMed: 22545178]
14. Prior R, Van Helleputte L, Benoy V, Van Den Bosch L. Defective axonal transport: A common pathological mechanism in inherited and acquired peripheral neuropathies. Neurobiol Dis 2017; 105: 300–320. [PubMed: 28238949]
15. Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, Hertz DL, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2020; 38: 3325–3348. [PubMed: 32663120]

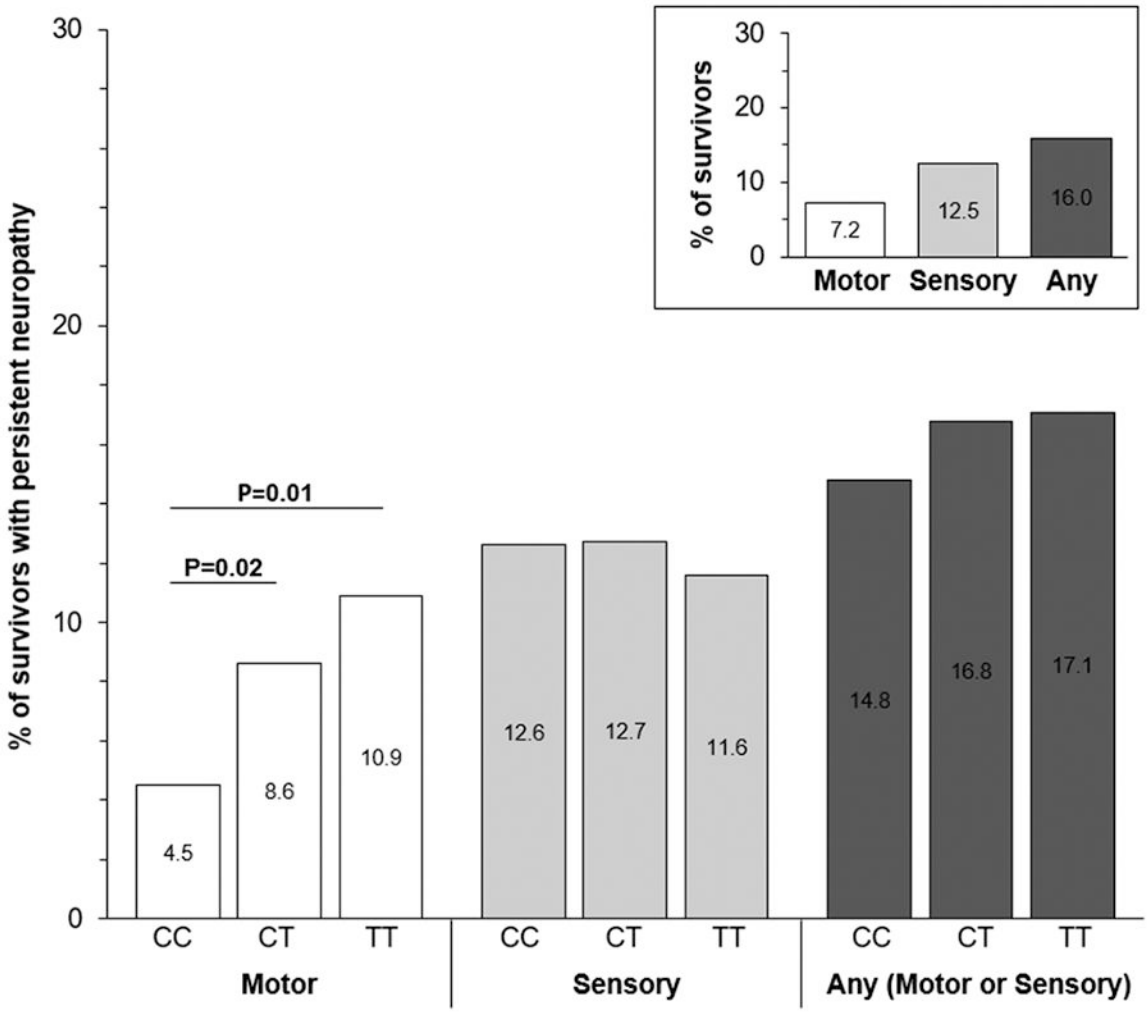


**Figure 1. Proportions of survivors with motor, sensory, or any (motor or sensory) persistent neuropathy (CTCAE Grade > 2) by CEP72 genotype (rs924607)**

Abbreviations: %, percent; P, probability

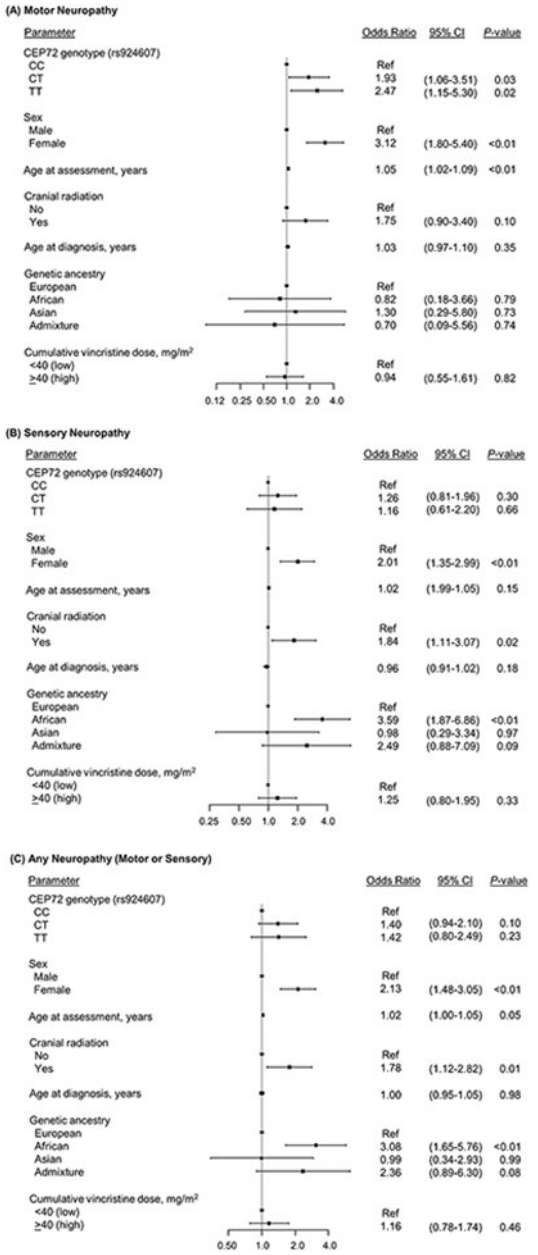


**Figure 2. Results of multivariate logistic regression model evaluating predictors of persistent neuropathy phenotypes (CTCAE Grade > 2) among 990 survivors**

Abbreviations: %, percent; CI, confidence interval; P, probability; ref, reference; <, less than; >, more than