SAGE Open Medical Case Reports
Volume 12: 1–4

DOI: 10.1177/2050313X241272534
journals.sagepub.com/home/sco
Sage

PML mutation and familial pediatric acute lymphoblastic leukemia: A case report

JinFang Zhang and MingYan Zhong

Abstract

Hereditary factors contribute to the pathogenesis of pediatric leukemia. However, few studies have reported gene mutation pathopoeias. This paper reports genetic mutations associated with hereditary acute lymphoblastic leukemia. We reported a case of siblings diagnosed with acute lymphoblastic leukemia when aged 3 and 7 years, both siblings are alive after chemotherapy, and whole exome sequencing analysis was performed on the siblings and their parents. It was observed that both siblings had diheterozygous mutations in *PML* gene (*PML*, NM_033250, exon7, c.2170A>G, p.S724G; *PML*, NM_033250, exon7, c.2195G>T, p.G732V), and their parents had heterozygous mutations in one mutation site of *PML* gene, respectively, suggesting that the diheterozygous mutations of *PML* gene might be causal genetic genes for the occurrence of acute lymphoblastic leukemia.

Keywords

PML mutation, hereditary, acute lymphoblastic leukemia

Date received: 13 April 2024; accepted: 15 July 2024

Introduction

Acute lymphoblastic leukemia (ALL) is the most common subtype of pediatric leukemia, and its pathogenesis is linked to gene mutations, impaired signal transduction, and chromosome mutations. Unlike adult ALL, pediatric ALL is highly influenced by genetic background.[1–3] Next-generation sequencing technology has led to the identification of hereditary factors that contribute to the initiation of pediatric ALL. Nevertheless, few studies have reported gene mutation pathopoeias. In this study, we report a case of siblings diagnosed with ALL and the application of next-generation sequencing analysis of the siblings and their parents.

Case presentation

Cases: Child A, a boy, was admitted to the hospital in August 2009 because of "recurrent low-grade fever and bone and joint pain for 1 month." The physical examination findings revealed a pale complexion, palpable swollen lymph nodes in the neck, a liver palpable 6 cm below the ribs, and a spleen palpable 5 cm below the ribs. The bone marrow examination indicated ALL of the B-cell type, with negative results for *BCR/ABL* and *IGH/MYC* by FISH analysis. The patient was treated following the GD-ALL-2008 protocol[4] and assigned to the medium-risk group. Child B, a girl, is the sibling sister of child A. She was admitted to the hospital in November 2017 because of "recurrent fever for 20 days." During the physical examination, the patient exhibited a pale complexion, with no swelling observed in superficial lymph nodes, and the liver and spleen appeared normal. Bone marrow examination indicated ALL of the B-cell type, with negative results for *BCR/ABL* and *MLL* detected by FISH analysis. The chromosome analysis revealed a 46, XX [10]/45, XX, -14[5] karyotype. The patient was treated with the SCCLG-ALL-2016 protocol[5] and assigned to the medium-risk group. Following treatment, the siblings were completely cured, and their bone marrow is currently in continuous remission until now. Family history showed no genetic history, the parents were healthy, and the father's uncle died of lung cancer.

Department of Paediatric Hematology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou City, Guangdong Province, China

Corresponding Author:
JinFang Zhang, Department of Paediatric Hematology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, No. 106 Zhongshan Second Road, Guangzhou City, Guangdong Province 510080, China.
Email: jinfangzhang1216@126.com

The siblings and their parents underwent whole exome sequencing (WES) using 2–3 mL of venous blood samples collected in ethylenediaminetetraacetic acid tubes containing anticoagulation.

Results

The results showed that both of the siblings were exposed to diheterozygous mutations in the *PML* gene (*PML*, NM_033250, exon7, c.2170A>G, p.S724G; *PML*, NM_033250, exon7, c.2195G>T, p.G732V). Their father had one heterozygous mutation (*PML*, NM_033250, exon7, c.2170A>G, p.S724G) of the *PML* gene, and their mother had another heterozygous mutation (*PML*, NM_033250, exon7, c.2195G>T, p.G732V) of the *PML* gene.

Discussion and conclusions

ALL remains an important cause of morbidity and mortality in children and adults. About 15%–20% of children with ALL experience a disease relapse. ALL aged 1–10 years has a good prognosis, while those younger than 1 year and older than 10 years have a relatively poor prognosis.[6,7] The immunophenotypes of the siblings diagnosed with ALL were all B-cell type and the siblings were categorized into the intermediate-risk group. Currently, the siblings have achieved remission following treatment with the pediatric ALL treatment regimen developed by the South China Regional Collaborative Group. We conducted WES on the siblings and their parents, revealing that the siblings harbored *PML* gene variants (*PML*, NM_033250, exon7, c.2170A>G, p.S724G; *PML*, NM_033250, exon7, c.2195G>T, p.G732V), with each parent carrying one of the variants. Hence, it is deduced that the *PML* gene variant may be the genetic causative gene and play a causative role in the development of ALL. There are currently no reports on the genetic pathogenesis of the *PML* gene.

The *PML* gene is primarily expressed in the *PML-RARA* fusion change, which is a characteristic alteration of acute promyelocytic leukemia. Currently, studies on *PML* mutation and leukemia have mainly focused on its pathogenesis and drug resistance mechanism with acute promyelocytic leukemia.[8] Located on Chromosome 15, the *PML* gene codes for a protein that is part of the triple structure domain protein family. Within this domain, there are three zinc finger binding regions, a loop, B-box 1 and B-box 2, and a convoluted helix region. This gene regulates various cellular processes, including tumor suppression, transcriptional regulation, apoptosis, and DNA damage.[9] It has been shown that promyelocytic leukemia (PML) can activate RB1 and inhibit AKT1 by phosphorylation of PP1 and PP2A, respectively, and block the mTOR/PI3K pathway to prevent the growth of tumor cells. PML can also regulate the transcriptional activity of ELF4 and act as an important mediator of tumor necrosis factor-alpha and interferon-alpha that regulates the formation and migration of endothelial cell networks.[10] The PML protein organizes nuclear aggregates known as PML nuclear bodies (PML-NBs), where many transcription factors localize to be regulated. PML NBs are implicated in a variety of human cancers ranging from leukemias to solid tumors, such as lung cancer, chronic myeloid leukemia, hepatocellular carcinoma, breast cancer, etc., this has led to the hypothesis that PML NBs might be important stress regulators in pathogenic conditions.[11] As for the children, PML-related tumors have occurred in children with glioma, bowel cancer, etc. The oncogenic role of PML is echoed in glioblastoma, Voon et al. found that H3.3 point mutations interfere with the formation of PML-NBs and, much like APL, these PML defects contribute to blocked differentiation in pediatric gliomas. H3.3 G34R mutation contributes to the formation of abnormal PML-NBs in pediatric gliomas with the *A*lternative *L*engthening of *T*elomeres phenotype.[12] PML is an important transcriptional regulator of pro-oncogenic metagenes in triple-negative breast cancer cells, via transcriptional regulation and epigenetic organization of heterochromatin domains that embed regions of local transcriptional activity.[13] Wan et al. showed that MAD1, which is upregulated in human breast cancer, displaces Mouse Double Minute 2 (MDM2) from PML to ubiquitinated P53, triggering tumorigenesis.[14]

The pathogenesis of leukemia is complex but it is not hereditary. Currently, the pathogenesis of acute leukemia involves fusion genes, gene mutation, gene expression abnormalities, and epigenetic alterations,[15,16] and several targeted drugs have been used to treat the corresponding genetic abnormalities. As an example, chronic myeloid leukemia is driven by *BCR-ABL* fusion genes, and the use of imatinib to target these genes has markedly enhanced long-term survival rates for this condition.[17] Nevertheless, tumor development is multifaceted and influenced by various factors, including the environment, inflammation, and individual genetic predisposition, all of which contribute significantly to the initiation and progression of tumors. In the case of childhood tumors, the genetic background factor contributes to the development of cancer.[18] Indeed, the probability of acute leukemia secondary to pediatric Down syndrome, Fanconi anemia, neurofibroma, and other diseases is significantly increased.[19] Advances in sequencing technology have led to the identification of several genetically related genetic abnormalities that participate in the pathogenesis of pediatric leukemia, mostly in isolated case reports or family studies. Furthermore, low penetrance or expression deletion of 7p12.2 (IKZF1), 9p12 (CDKN2A/CDKN2B), 10q21.2 (ARID5B), and 14q11.2 (CEBPE) has been linked to the family and hereditary nature of pediatric B-ALL.[20] For inherited bone marrow failure syndromes such as Fanconi anemia, aberrant expression of related genes (e.g., *FANCA, FANCP/SLX4*) has been associated with familial ALL onset or transformation.[21] Research on acute myeloid leukemia has revealed associations between mutations in inherited bone

marrow failure syndrome-related genes, such as *FANCC* and *CHEK2*, and childhood-onset familial AML.[22] Moreover, a double mutation in *CEBPA* has been identified as a gene linked to the development of AML.[23] In this paper, we identified a pair of siblings who were diagnosed with acute B-lymphoblastic leukemia successively, and linked to the hereditary factor based on analysis of environmental, dietary, and other related factors. Results of next-generation sequencing showed that both siblings had diheterozygous mutations in the *PML* gene, while their parents had heterozygous mutations in one mutation site of the *PML* gene, and their father's uncle passed away due to lung cancer. Previous reports have linked *PML* mutations to the development of lung cancer.[24] *PML* mutations have not been previously reported to be associated with the development of acute lymphocytic leukemia, and the pathogenicity and significance of the variants found have not been functionally analyzed and are currently unknown. Whether gene mutation causes disease is a very complex mechanism. We used the ClinVar database to predict *PML* mutation and function, but the results showed that the two sites were benign changes; however, whether both sites together changed could change the protein structure is not clear. Judging from the results of the case, it should be pathogenic but needs further experimental verification.

Consequently, it is postulated that diheterozygous mutations in the *PML* gene may contribute to the onset of ALL and may have a hereditary component. However, the connection between this gene mutation and familial ALL remains unexplored, and the pathogenicity of this mutation needs to be validated through functional studies.

Acknowledgements

Many thanks to parents for supporting the publication of clinical data.

Author contributions

J.F.Z. designed the study, carried out the statistical analysis and provided the data, drafted the initial manuscript, and approved the final manuscript as submitted. M.Y.Z. reviewed the manuscript and approved the final manuscript as submitted.

Data availability

All data generated or analyzed during this study are included in the submitted article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by funding from the Guangdong Medical Research Foundation (Grant number A2022349).

Ethics considerations

The study was approved by the Ethics Committee Board of the Guangdong Provincial People's Hospital (KY-Q-2021-623-03).

Consent to participate

Informed consent was obtained from parents and legal guardians.

Consent for publication

All authors are in agreement with the content of the manuscript.

ORCID iD

JinFang Zhang https://orcid.org/0000-0001-7734-2226

References

1. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat Rev Cancer* 2018; 18(8): 471–484.
2. Inaba H and Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica* 2020; 105(11): 2524–2539.
3. Bhojwani D, Yang JJ and Pui CH. Biology of childhood acute lymphoblastic leukemia. *Pediatr Clin North Am* 2015; 62(1): 47–60.
4. Que LP, Huang K, Fang JP, et al. Reassessment of the Risk-stratified GD-2008 ALL protocol. *J Pediatr Hematol Oncol* 2018; 40(6): 472–477.
5. Wang J, Jia WG, Yang LH, et al. Clinical summary of pediatric acute lymphoblastic leukemia patients complicated with asparaginase-associated pancreatitis in SCCLG-ALL-2016 protocol. *Hematology* 2023; 28(1): 2171723.
6. Hunger SP and Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med* 2015; 373(16): 1541–1552.
7. Dini G, Capolsini I, Cerri C, et al. Acute lymphoblastic leukemia relapse presenting with optic nerve infiltration. *SAGE Open Med Case Rep* 2023; 11: 2050313X231175020.
8. Jimenez JJ, Chale RS, Abad AC, et al. Acute promyelocytic leukemia (APL): a review of the literature. *Oncotarget* 2020; 11(11): 992–1003.
9. Chang HR, Munkhjargal A, Kim MJ, et al. The functional roles of PML nuclear bodies in genome maintenance. *Mutat Res* 2018; 809: 99–107.
10. Cohen N, Sharma M, Kentsis A, et al. PML RING suppresses oncogenic transformation by reducing the affinity of eIF4E for mRNA. *EMBO J* 2001; 20(16): 4547–4559.
11. Li Y, Ma X, Wu W, et al. PML nuclear body biogenesis, carcinogenesis, and targeted therapy. *Trends Cancer* 2020; 6(10): 889–906.
12. Voon HPJ, Hii L, Garvie A, et al. Pediatric glioma histone H3.3 K27M/G34R mutations drive abnormalities in PML nuclear bodies. *Genome Biol* 2023; 24(1): 284.
13. Fracassi C, Ugge' M, Abdelhalim M, et al. PML modulates epigenetic composition of chromatin to regulate expression of pro-metastatic genes in triple-negative breast cancer. *Nucleic Acids Res* 2023; 51(20): 11024–11039.
14. Wan J, Block S, Scribano CM, et al. Mad1 destabilizes p53 by preventing PML from sequestering MDM2. *Nat Commun* 2019; 10(1): 1540.
15. Kayser S and Levis MJ. Clinical implications of molecular markers in acute myeloid leukemia. *Eur J Haematol* 2019; 102(1): 20–35.

16. Hein D, Borkhardt A and Fischer U. Insights into the prenatal origin of childhood acute lymphoblastic leukemia. *Cancer Metastasis Rev* 2020; 39(1): 161–171.
17. Apperley JF. Chronic myeloid leukaemia. *Lancet* 2015; 385(9976): 1447–1459.
18. Pui CH, Nichols KE and Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. *Nat Rev Clin Oncol* 2019; 16(4): 227–240.
19. Saida S. Predispositions to leukemia in down syndrome and other hereditary disorders. *Curr Treat Options Oncol* 2017; 18(7): 41.
20. Bloom M, Maciaszek JL, Clark ME, et al. Recent advances in genetic predisposition to pediatric acute lymphoblastic leukemia. *Expert Rev Hematol* 2020; 13(1): 55–70.
21. Spinella JF, Healy J, Saillour V, et al. Whole-exome sequencing of a rare case of familial childhood acute lymphoblastic leukemia reveals putative predisposing mutations in Fanconi anemia genes. *BMC Cancer* 2015; 15: 539.
22. Berger G, van den Berg E, Smetsers S, et al. Fanconi anaemia presenting as acute myeloid leukaemia and myelodysplastic syndrome in adulthood: a family report on co-occurring FANCC and CHEK2 mutations. *Br J Haematol* 2019; 184(6): 1071–1073.
23. Tawana K, Wang J, Renneville A, et al. Disease evolution and outcomes in familial AML with germline CEBPA mutations. *Blood* 2015; 126(10): 1214–1223.
24. Kuo HY, Huang YS, Tseng CH, et al. PML represses lung cancer metastasis by suppressing the nuclear EGFR-mediated transcriptional activation of MMP2. *Cell Cycle* 2014; 13(19): 3132–3142.