



# Is There a Genetic Relationship between Acute Lymphoblastic Leukemia and Meningioma? A Case Report of the Analyses of Three Genes

## *Há alguma relação genética entre leucemia linfoblástica aguda e meningioma? Relato de caso das análises de três genes*

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### Abstract

Meningiomas are the most common tumors of the central nervous system, and they are generally slow growing and benign. Acute lymphoblastic leukemia (ALL) is a life-threatening type of cancer that involves the accumulation of peripheral blood vessels and immature cells in the bone marrow. Genetic mutations play an important role in the etiology of both diseases. Therefore, in the case herein presented, we investigated the *meningioma 1 (MN1)*, *nucleophosmin 1 (NPM1)*, and *Wilms tumor 1 (WT1)* genes for possible genetic mutations. A 27-year-old female with a chief complaint of headache and history of ALL presented with a mass in the left frontal lobe. The pathological analysis revealed a fibroblastic meningioma. However, the three genes were found to be normal in the analysis. In light of these findings, we did not encounter any evidence of a genetic relationship between meningioma and ALL in the present study.

### Keywords

- ▶ acute lymphoblastic leukemia
- ▶ meningioma
- ▶ MN1
- ▶ NPM1
- ▶ WT1

### Resumo

Os meningiomas são os tumores mais comuns do sistema nervoso central e geralmente apresentam crescimento lento e são benignos. A leucemia linfoblástica aguda (LLA) é um tipo de câncer com risco de vida que envolve o acúmulo de vasos sanguíneos periféricos e células imaturas na medula óssea. As mutações genéticas desempenham um papel importante na etiologia de ambas as doenças. Portanto, no caso aqui apresentado, investigamos os genes do meningioma 1 (MN1), nucleofosmina 1 (NPM1) e tumor de Wilms 1 (WT1) para possíveis mutações genéticas. Uma mulher de 27 anos com queixa principal de cefaleia e história de LLL apresentou uma massa no lobo frontal esquerdo. A análise anatomopatológica revelou um meningioma fibroblástico. No entanto, os três genes foram considerados normais na análise. À luz desses achados, não encontramos nenhuma evidência de relação genética entre meningioma e LLA no presente estudo.

### Palavras-chave

- ▶ linfoblástico agudo leucemia
- ▶ MN1
- ▶ NPM1
- ▶ WT1

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## Introduction

Meningiomas are widespread primary central nervous system tumors originating from the arachnoid cap cells. The growth rate of meningiomas is usually considered slow that associated with low mortality and high morbidity. Genetic mutations have been reported to play a role in the development of meningiomas.<sup>1</sup>

Acute lymphoblastic leukemia (ALL) is a life-threatening malignant tumor involving the accumulation of lymphoblast cells in hematopoietic tissues such as the bone marrow, the spleen, the peripheral blood, and the lymph nodes.<sup>2</sup> LLIt is the most common type of acute leukemia in pediatric patients, accounting for ~ 25% of childhood malignancies. In addition, ALL is responsible for 20% of adult acute leukemia.<sup>2</sup> LLThe etiology of ALL probably environmental, socioeconomic, infectious, and genetic factors are currently under investigation.

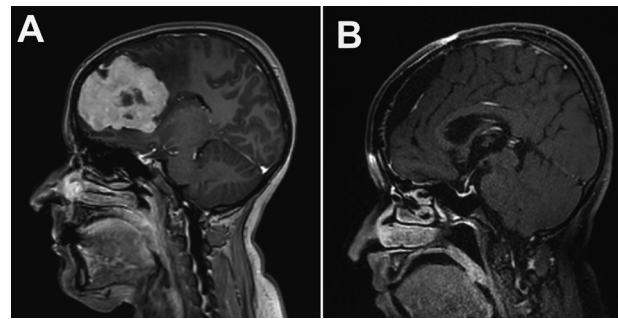
The *meningioma 1 (MN1)* gene is a transcriptional coactivator encoding a 136 kDa protein located in the 22q12 chromosome.<sup>3</sup> The *MN1* gene was first identified as part of a translocation in meningiomas.<sup>4</sup> Overexpression of this gene is related to poor prognosis, poor treatment response, and short survival. Further, it has been reported that *MN1* overexpression plays an important role in acute myeloblastic leukemia (AML), and is associated with poor clinical outcomes in normal-karyotype AML.<sup>5</sup>

The *Wilms tumor 1 (WT1)* gene encodes a C2H2-type zinc finger transcription factor located in the 11p13 chromosome, and is known to present distinct isoforms in mammals.<sup>6</sup> Further, it is involved in processes such as transcriptional regulation, RNA metabolism, and participation in protein-protein interactions.<sup>6</sup> The *WT1* gene was first described in AML overexpression, a childhood malignancy.<sup>3</sup> Although *WT1* is not associated with a specific leukemic disease, many studies have reported that this gene may be a sensitive parameter in the onset or reappearance of the disease.<sup>7</sup> In adults, *WT1* overexpression leads to lung, brain and breast cancers.<sup>7</sup>

The *nucleophosmin 1 (NPM1)* gene is located in chromosome 5q35. It is composed of 12 exons and a histone chaperone that can bind to broad H3-H4 tetramers and can constitute nucleosomes in chromatins.<sup>8</sup> The associated proteins bind to histones and transfer them to the naked DNA.<sup>8</sup> Overexpression of the *NPM1* gene results in high mitotic index and proliferation. This can lead to solid organ tumors like oral, prostate, ovary, colon, and bladder cancers.

Several studies have reported on the *MN1*, *NPM1*, and *WT1* genes. Associations between *MN1* gene mutations and AML have been frequently investigated, and there are studies that report poor prognosis.<sup>9</sup> The relationship of the *MN1* gene with meningiomas has also been reported.<sup>4</sup> However, in the literature, we could not find any studies reporting a relationship between the *MN1*, *NPM1*, and *WT1* genes and ALL; no association between meningiomas and ALL has been identified.

We examined a young female with a history of ALL who underwent surgery for a convexity meningioma at our clinic. We investigated the possible gene mutations, such as those in the *MN1*, *WT1*, and *NPM1* genes, to determine whether there is an association between ALL and meningiomas.



**Fig. 1** Contrast-enhanced cranial magnetic resonance imaging identified a 66cm<sup>2</sup> calcified mass in the left frontal lobe (A). When the patient's history was examined, it was found that B-cell common ALL (CALLAB) had been diagnosed and treated 10 years prior to presentation. The intraoperative mass was totally resected, and there were no complications. Remarkably, the patient's headache and visual complaints improved, and no recurrence was observed during the follow-up visit 1 year postoperatively (B).

## Case Report

A 27-year-old female presented to our clinic with headache and blurred vision. No motor and sensory deficits were detected on the physical examination. Further, the cranial nerves were intact. Contrast-enhanced cranial magnetic resonance imaging identified a 6 × 6 cm<sup>2</sup> calcified mass in the left frontal lobe (► Fig. 1 A). When the patient's history was examined, it was found that B-cell common ALL (CALLA-B) had been diagnosed and treated 10 years prior to presentation. The intraoperative mass was totally resected, and there were no complications. Remarkably, the patient's headache and visual complaints improved, and no recurrence was observed during the follow-up visit 1 year postoperatively (► Fig. 1 B). The pathology report was interpreted as fibroblastic meningioma (Grade 1). The patient had not received radiotherapy before, and intrathecal medication was not administered.

An *MN1* gene mutation has been detected in meningioma and AML. However, there are insufficient articles in the literature about common gene mutations that coexist in meningiomas and ALL. A peripheral blood sample and paraffin block preparation were transferred to the gene analysis laboratory to investigate the *MN1*, *WT1*, and *NPM1* genes.

## Analysis of the DNA Sequence I

Genomic DNA was isolated from the paraffin block with the use of the QIAamp DNA FFPE Tissue Kit (Qiagen inc., Hilden, Germany), and from the peripheral blood sample with the QIAamp DNA Blood Mini Kit (Qiagen, Inc.), according to the manufacturer's instructions. The DNA isolates are stored at -20°C until the polymerase chain reaction (PCR) step. The primers were designed for the coding and exon-intron junction regions of the three genes: *WT1* (NM\_024426, ENST00000452863), *MN1* (NM\_002430, ENST00000302326), and *NPM1* (NM\_002520, ENST00000296930). In total, 10 pairs of PCR primers were designed to amplify 10 coding exons of the *WT1* gene, 3 pairs, to amplify 2 coding exons of the *MN1* gene, and 8 pairs, to amplify 11 coding exons of the *NPM1* gene. The PCRs were performed on isolated DNA samples using the

designed primers and the MyTaq Mix (Illumina Biosciences, Cincinnati, OH, US) according to the manufacturer's instructions. The reactions were examined using 2% agarose gel electrophoresis. The PCR products from the same sample were combined to obtain PCR pools, and they were purified with the NucleoFast 96 PCR kit, (Macherey-Nagel GmbH & Co., Dueren, Germany). The purified PCR pools were quantified with the ND1000 microvolume spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, US), and standardized to 0.2 ng/ul, which was needed for sample preparation. The samples were prepared for next-generation sequencing with the NexteraXT I (Illumina, Inc., San Diego, CA, US) sample preparation kit, and they were subsequently sequenced with the Miseq system (Illumina, Inc.). The data were visualized and analyzed with the IGV 2.3 software (Broad Institute, Cambridge, MA, US), to search for possible pathogenic mutations.

As a result of these DNA analyses, no clinically important mutations of the *MN1*, *WT1* and *NPM1* genes were detected.

## Discussion

Meningiomas are the most common benign intracranial lesion. Although the etiology of meningiomas remains unclear, various proto-oncogenes and tumor-suppressor genes have been reported to play a role.<sup>1</sup>

The subtypes of ALL may differ in terms of biological, cellular, and molecular characteristics, treatment response, and risk of relapse, and they usually present different outcomes.<sup>10</sup> B-cell precursor ALL (BCP-ALL) is a disease characterized by the proliferation of the blast forms of immature B cells in the bone marrow and/or peripheral bone, which can be caused by some known molecular changes.<sup>11</sup> Reportedly, the Epstein-Barr virus and human immunodeficiency virus (HIV) type 1 are closely related to the underlying infectious agents in the etiology of BCP-ALL.<sup>12</sup> Our patient, who was diagnosed with BCP-ALL, had no history of infection.

Although the mechanism of action of the *MN1* gene and its contribution to leukemogenesis are not completely known, its overexpression has been reported to cause myeloid malignancies.<sup>5</sup> The *MN1* gene mutation has also been reported in meningiomas.

It is unclear how the *WT1* gene contributes to malignant transformation in adults.<sup>6</sup> However, it is known that the gene plays a role in processes such as apoptosis, proliferation, differentiation, and mRNA processing in the genitourinary system, sensory system, and heart cells in the wide embryological process.

The *NPM1* gene plays an important role in RNA transport, ribosome biogenesis, regulation of apoptosis, and genomic hemostasis in large cells.<sup>13</sup> Its mutation or fusion is predominantly observed in acute myeloid leukemia, and it is present in ~30% of the patients. Overexpression of the *NPM1* gene is associated with poor prognosis and malignancies such as glioblastoma multiforme, oral squamous cell carcinoma, colon cancer, non-small cell lung cancer, hepatocellular carcinoma, ovarian cancer, and endometrial carcinoma, in addition to leukemia.<sup>13</sup>

Carturan et al.<sup>9</sup> studied the *MN1*, *WT1*, and *NPM1* genes in 136 patients with AML and 50 healthy volunteers, and, according to their study, overexpression of these genes is indicative of poor prognosis in patients with AML.

Is there a relationship between meningiomas and ALL, or is it a random association? We examined a possible molecular genetic mutation in this patient who presented with leukemia and meningiomas. A genetic analysis of the tumor tissue and blood sample identified *CALLA-B* and fibroblastic meningioma. The *MN1*, *WT1*, and *NPM1* genes were analyzed and found to be normal.

Although we cannot have a definitive understanding about the relationship between these two diseases based on a single case, our case can trigger future studies. Since the number of cases has been increasing, the relationship between these two diseases is expected to become clearer. Therefore, large-scale clinical trials are needed.

## Conflict of Interests

The authors have no conflict of interests to declare.

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