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Research Article

H3F3B gene mutation in chondroblastomas: a multicenter study

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ABSTRACT

Objective: Chondroblastoma (CB) is a benign but locally aggressive bone tumor that may present histopathologic diagnostic challenges, particularly in atypical locations and limited biopsy specimens. Recent studies have identified recurrent mutations in the *H3F3B* and, less frequently, *H3F3A* genes, suggesting their potential diagnostic value. This study aimed to evaluate the prevalence and diagnostic utility of *H3F3A* and *H3F3B* mutations in a multicenter cohort of CB patients.

Methods: Forty-three patients with histopathologically confirmed CB were included in a retrospective analysis. All cases were re-evaluated by 2 pathologists, and mutation analysis of *H3F3A* and *H3F3B* genes was performed using polymerase chain reaction–based Sanger sequencing.

Results: *H3F3B* mutations were detected in 41 cases (95.3%), all corresponding to the Lys36Met substitution. One case (2.3%) harbored an *H3F3A* Gly34Trp mutation, whereas 1 case (2.3%) showed no detectable mutation. No significant histopathological differences were observed between mutation-positive and mutation-negative cases. A notable case involved a 72-year-old patient with frontal bone involvement, highlighting the diagnostic difficulty in unusual locations and older age groups.

Conclusion: The findings demonstrate that *H3F3B* mutation analysis is an extremely sensitive and reliable molecular tool for confirming the diagnosis of CB. It is particularly valuable in challenging cases and especially in small biopsy samples where pathognomonic findings, such as chicken-wire calcification and chondroid matrix are not visible. Incorporation of molecular testing into targeted diagnostic workflows may improve diagnostic accuracy and assist in distinguishing CB from its histological mimics.

Level of Evidence: Level IV, Diagnostic study.

Introduction

Chondroblastoma (CB) is a benign but locally aggressive bone tumor that accounts for 1%-2% of all primary bone tumors. It has a strong predilection for the epiphyseal or apophyseal regions of long bones, typically occurring in children and young adults before epiphyseal closure.[1,2] Histologically, it is composed of chondroblastic cells, islands of eosinophilic chondroid matrix, and characteristic chicken wire calcification interspersed with multinucleated osteoclast-like giant cells.[3] Radiologically, CB characteristically presents as an osteolytic, epi-metaphyseal lesion with a narrow zone of transition, lobulated contours, and a thin sclerotic rim. Computed tomography imaging, particularly in the bone window, typically demonstrates this sclerotic margin along with internal chondroid-type calcifications.[4]

Despite these characteristic features, histopathological diagnosis of CB may be challenging, particularly in atypical locations and small biopsy specimens. Recent studies have identified somatic driver mutations in the *H3F3A and H3F3B* histone genes, which are present in 92% of giant cell tumors of bone (GCTB) and 95% of CB lesions, respectively.[5]Specifically, *H3F3B* mutations have been detected in over 90% of CBs, while *H3F3A* mutations are rare.[5,6] Although *H3F3A* and *H3F3B* encode the same H3.3 histone protein, there is an ongoing discussion in the literature regarding their striking tumor-type specificity. Despite producing an identical protein, mutations in these genes are associated with distinct neoplastic entities, suggesting that factors such as cellular context, epigenetic landscape, and lineage-specific expression patterns may play a critical role. Furthermore, it remains unclear whether these mutations act merely as diagnostic markers or represent true oncogenic drivers contributing to tumorigenesis. This unresolved distinction continues to be an area of active investigation.[5] Therefore, this multicenter study aims to investigate the prevalence of *H3F3B* and *H3F3A* mutations in patients diagnosed with CB and to evaluate their diagnostic utility especially in atypical cases.

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Material and methods

This retrospective, multicenter study was conducted across 8 pathology departments between 2011 and 2021. The research was performed in accordance with the ethical guidelines outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Ümraniye Training and Research Hospital (Approval number: B.10.1.TKH.4.34.H.GP.0.01/162, Date: 28.05.2021).

Slides and formalin-fixed paraffin-embedded tissue blocks from patients diagnosed with CB were collected. Two independent pathologists performed a histopathological re-evaluation of the bone specimens to confirm the diagnosis of CB. The *H3F3A and H3F3B* genes were analyzed using polymerase chain reaction (PCR)-based Sanger sequencing on appropriate tissue blocks. Patients for whom molecular analysis could not be successfully performed due to extensive bone decalcification were excluded from the study.

Mutation analysis

Mutations in exon 2 of the *H3F3A* and *H3F3B* genes were analyzed using PCR-based Sanger sequencing. DNA concentrations were measured spectrophotometrically using a Nanodrop 1000 spectrophotometer (ThermoScientific, USA). Bidirectional sequencing traces were analyzed using SeqScape v3.0 software (Applied Biosystems, Thermo Fisher Scientific Inc., Foster City, CA, USA) and manually reviewed against the reference sequences of *H3F3A* (NM_002107.7) and *H3F3B* (NM_005324.5).

Results

A total of 43 patients with a histopathological diagnosis of CB were included in the study. Demographic data, tumor location, and mutation status are summarized in Table 1. The mean age of the patients was 17 years (range: 2-72 years), with 27 males and 16 females. The tumors were in the femur (n=20), followed by tibia (n=7), humerus (n=6), talus (n=4), patella (n=4), calcaneus (n=1), and frontal bone (n=1).

Tru-cut biopsy was performed in only 1 patient, while curettage materials were obtained from the remaining patients. Four patients had recurrent tumors, while the others had primary tumors. Histopathological examination confirmed the diagnosis of CB in all cases (Figure 1).

Polymerase chain reaction–based Sanger sequencing revealed *H3F3B* mutations in 41 patients (95.3%) (Figure 2) and an *H3F3A* mutation in 1 patient (2.3%). The Lys36Met alteration was detected in the *H3F3B* gene in 41 cases, while the *H3F3A* gene showed a Gly34Trp alteration in 1 case. One patient (2.3%) had no detectable mutation in either gene. All patients, regardless of their mutation status, showed typical histomorphological features consistent with CB, and no significant histopathological differences were observed between the *H3F3B* mutation-positive, *H3F3A* mutation-positive, and mutation-negative cases.

The patient harboring the *H3F3A* mutation was a 16-year-old boy who presented with a calcaneal mass. Magnetic resonance imaging (MRI) revealed a lesion that completely occupied the calcaneus, destroying the bone structure and containing hyperdense areas compatible with calcification, with widespread cystic openings measuring up to 96 × 72 × 65 mm in size (Figure 3). Microscopically, the tumor demonstrated typical CB features with polygonal chondroblasts showing characteristic nuclear grooves, multinucleated giant cells, and areas of chondroid matrix formation (Figure 4).

The mutation-negative patient in the study was a 23-year-old man with a tibial tumor. Magnetic resonance imaging revealed an irregular, well-demarcated mass measuring 20 × 17 × 12 mm in the posteromedial condyle of the tibia, with focal cortical destruction. Microscopically, the tumor exhibited classic histopathological features of CB, including sheets of polygonal cells with nuclear grooves, scattered multinucleated giant cells, and characteristic chicken-wire calcification pattern, confirming the diagnosis despite the absence of detectable mutations (Figure 5).

The most notable case in the cohort was a patient with frontal bone involvement, who was also the oldest participant. This 72-year-old woman presented with a 1-year history of progressive vision loss. Brain MRI detected a well-defined, heterogeneously enhancing lesion extending from the ethmoid bone to the inferior aspect of the frontal lobe, displaying characteristic signal intensity patterns (Figure 6). Microscopically, the tumor showed classic features of CB, with polygonal chondroblasts exhibiting characteristic nuclear grooves and moderate cytoplasmic eosinophilia. The tumor cells were arranged in sheets with interspersed multinucleated giant cells and areas of chondroid matrix formation. The characteristic chicken-wire calcification pattern was also prominently observed (Figure 7).

Discussion

The histopathological diagnosis of CB can be straightforward in classic cases presenting with typical morphology and characteristic radiological findings. However, the differential diagnosis becomes significantly challenging when tumors occur in atypical anatomical locations, present in older age groups, or when only limited biopsy material is available. In such scenarios, distinguishing CB from other giant cell-rich or chondroid lesions is critical. Therefore, molecular studies, particularly the identification of *H3F3B* mutations, have gained immense importance in recent years as a reliable diagnostic adjunct.[7]

The *H3F3A* and *H3F3B* genes are located at 1q42.12 and 17q25.1, respectively, and encode identical H3.3 core histone proteins. Mutations in these genes play a significant role in the pathogenesis of specific bone and brain tumors.[8] Behjati et al reported p. Lys36Met alterations in the *H3F3B* gene in 95% of CB cases and the *H3F3A* gene in 92% of GCTB.[5] Consistent with the literature, the study demonstrated a high prevalence of *H3F3B* mutations, detecting the Lys36Met alteration in 95.3% (41/43) of the CB cohort, while an *H3F3A* mutation (Gly34Trp) was observed in only 1 case.

Other studies have corroborated these high mutation frequencies. Cleven et al investigated the frequency of *H3F3A*, *H3F3B*, *IDH1*, and

HIGHLIGHTS

- Chondroblastoma (CB) is a rare benign bone tumor that can present significant diagnostic challenges, particularly in atypical locations or limited biopsy specimens.
- Giant cell lesions of bone and cartilage create difficulties in the differential diagnosis.
- *H3F3B* gene mutations (p. Lys36Met) are highly prevalent in CB and serve as an extremely sensitive molecular diagnostic marker.
- *H3F3B* mutation testing is most clinically valuable in diagnostically challenging scenarios, such as skull base involvement, older age groups, or when distinguishing CB from malignant mimics like CB-like osteosarcoma.

Table 1. Demographic data of the cases

Case	Age (years)	Sex	Location	Specimen	Recurrence	*H3F3B* Mutation	*H3F3A* Mutation
1	22	Male	Right talus	Curettage	No	Positive	Negative
2	23	Male	Left proximal tibia	Curettage	No	Negative	Negative
3	17	Female	Right proximal tibia	Curettage	Yes	Positive	Negative
4	17	Female	Right proximal humerus	Tru-cut	No	Positive	Negative
5	15	Female	Right proximal humerus	Curettage	Yes	Positive	Negative
6	15	Male	Right proximal femur	Curettage	Yes	Positive	Negative
7	25	Male	Right femur	Curettage	No	Positive	Negative
8	32	Male	Proximal femur	Curettage	No	Positive	Negative
9	20	Male	Right distal femur	Curettage	No	Positive	Negative
10	72	Female	Frontal bone	Curettage	No	Positive	Negative
11	17	Female	Distal femur	Curettage	No	Positive	Negative
12	27	Male	Left talus	Curettage	No	Positive	Negative
13	25	Male	Right proximal tibia	Curettage	No	Positive	Negative
14	12	Female	Right distal femur	Curettage	No	Positive	Negative
15	25	Male	Patella	Curettage	No	Positive	Negative
16	17	Male	Right proximal tibia	Tru-cut	No	Positive	Negative
17	16	Male	Left proximal humerus	Curettage	No	Positive	Negative
18	24	Female	Right distal femur	Curettage	No	Positive	Negative
19	17	Male	Left proximal tibia	Curettage	No	Positive	Negative
20	11	Female	Medial condyle of right knee	Curettage	No	Positive	Negative
21	16	Male	Calcaneus	Curettage	No	Negative	Positive
22	21	Male	Talus	Curettage	No	Positive	Negative
23	22	Female	Proximal femur	Curettage	No	Positive	Negative
24	27	Female	Talus	Curettage	No	Positive	Negative
25	15	Male	Proximal humerus	Curettage	No	Positive	Negative
26	21	Male	Proximal humerus	Curettage	No	Positive	Negative
27	14	Male	Femoral head	Curettage	No	Positive	Negative
28	17	Female	Distal femur	Curettage	No	Positive	Negative
29	14	Male	Distal femur	Curettage	No	Positive	Negative
30	14	Female	Epiphysis of the right knee	Curettage	No	Positive	Negative
31	19	Male	Distal femur	Curettage	No	Positive	Negative
32	12	Female	Femur trochanter	Curettage	No	Positive	Negative
33	16	Male	Medial condyle of femur	Curettage	No	Positive	Negative
34	16	Male	Distal femur	Curettage	No	Positive	Negative
35	29	Male	Proximal humerus	Curettage	No	Positive	Negative
36	19	Male	Proximal tibia	Curettage	No	Positive	Negative
37	39	Female	Femur	Curettage	No	Positive	Negative
38	16	Female	Distal femur	Curettage	No	Positive	Negative
39	17	Male	Medial condyle of femur	Curettage	No	Positive	Negative
40	21	Male	Patella	Curettage	No	Positive	Negative
41	21	Male	Proximal tibia	Curettage	No	Positive	Negative
42	34	Male	Distal femur	Curettage	No	Positive	Negative
43	33	Female	Femur	Curettage	No	Positive	Negative

IDH2 mutations in GCTB, CB, and other giant cell–containing tumors using Sanger sequencing.[9] They found that 70% of CB cases harbored *H3F3B* mutations, with no mutations detected in other giant cell-containing tumors. In another study comparing CB patients with those suspected of having CB, immunohistochemical analysis revealed significant differences in H3K36M staining, with PCR results consistent with immunohistochemical findings.[10] Among patients with suspected CB, no *H3F3B* mutations were detected, while 1 patient with a giant cell tumor had a *G34W* mutation. Amary et al evaluated the expression of the K36M-mutated protein in 85 CB patients, identifying *H3F3* p.K36M mutations in 82 patients, with only 3 lacking *H3F3A/H3F3B* mutations.[11] In the study, 41 of 43 patients with a histomorphologically confirmed diagnosis of CB had *H3F3B* mutations detected by PCR-based Sanger sequencing, yielding a sensitivity of 95%. One patient (2.3%) had an *H3F3A* mutation, consistent with previous studies. Behjati et al also identified *H3F3A* mutations in 5 of 73 CB cases.[5] It is acknowledged that immunohistochemical analysis has several important advantages including lower cost, wider availability, and easier interpretation in routine practice. Although immunohistochemical analysis has high specificity and sensitivity for CB diagnosis, mutation analysis method was used, which is considered the gold standard for molecular diagnosis, in this study. Both methods have complementary roles in the diagnostic workup of CB, and the choice between them may depend on institutional resources and clinical context.

The clinical implications of *H3F3B* mutation analysis become particularly evident in atypical presentations, such as skull base involvement. The cohort included a 72-year-old female with a CB extending from the ethmoid bone to the frontal lobe. To the best of current knowledge, only 1 other case of CB with frontal bone involvement has been reported in the literature, which involved

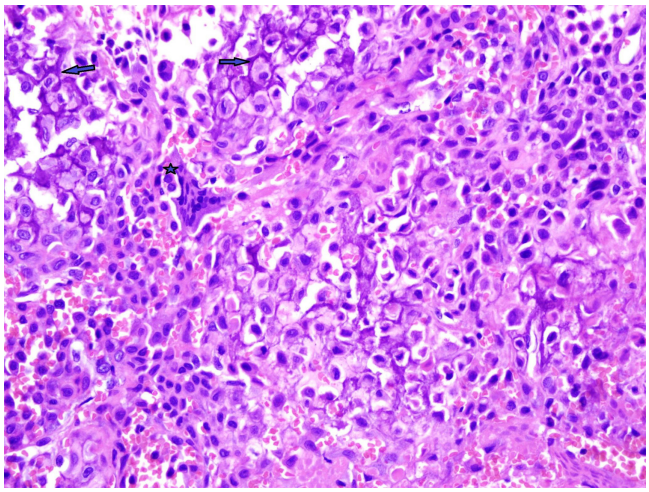


Figure 1. Histopathological examination of chondroblastoma demonstrating characteristic pericellular "chicken-wire" calcification (arrows) and interspersed multinucleatedgiant cells (asterisk) (H&E, ×40).

an 8-year-old child.[12] Therefore, the patient represents the second reported case with this unusual location, and notably, the first in an elderly patient. Given their rarity—especially in older individuals—skull base CBs are frequently misdiagnosed as chordomas, meningiomas, or other skull base tumors, as they are not typically considered in the initial differential diagnosis.[13] Although skull base CBs may radiologically mimic chordomas and meningiomas, certain features aid in differentiation. Chordomas typically show midline localization and markedly high T2 signal intensity, whereas meningiomas are extra-axial lesions with hyperostosis and a dural tail sign.[14] In contrast, CBs tend to present as well-defined osteolytic lesions with possible chondroid calcifications and lower T2 signal intensity.[4] Nevertheless, significant radiological overlap exists. In such unusual locations and age groups, *H3F3B* mutation testing serves as a definitive molecular tool to confirm the diagnosis and prevent unnecessary aggressive treatments.[15]In chondroblastomas, satisfactory functional outcomes can be achieved even in cases of recurrence through early diagnosis, aggressive curettage, and the use of local adjuvants, with grafting remaining the first-line reconstructive option.[16]

The histopathological differential diagnosis of CB primarily includes GCTB, aneurysmal bone cysts, chondromyxoid fibromas, clear cell chondrosarcomas, and CB-like osteosarcomas.[17] These tumors may exhibit overlapping morphological features, such as the presence of osteoclast-like giant cells, chondroid or myxoid matrix, and variable cellular atypia. Molecular analyses are highly valuable for differentiating these challenging entities. For instance, detecting *H3F3A* mutations supports a diagnosis of GCTB,[18,19] while *USP6* gene rearrangements are characteristic of primary aneurysmal bone cysts,[20] and *GRM1* upregulation is seen in chondromyxoid fibromas.[21] Furthermore, distinguishing CB from CB-like osteosarcoma

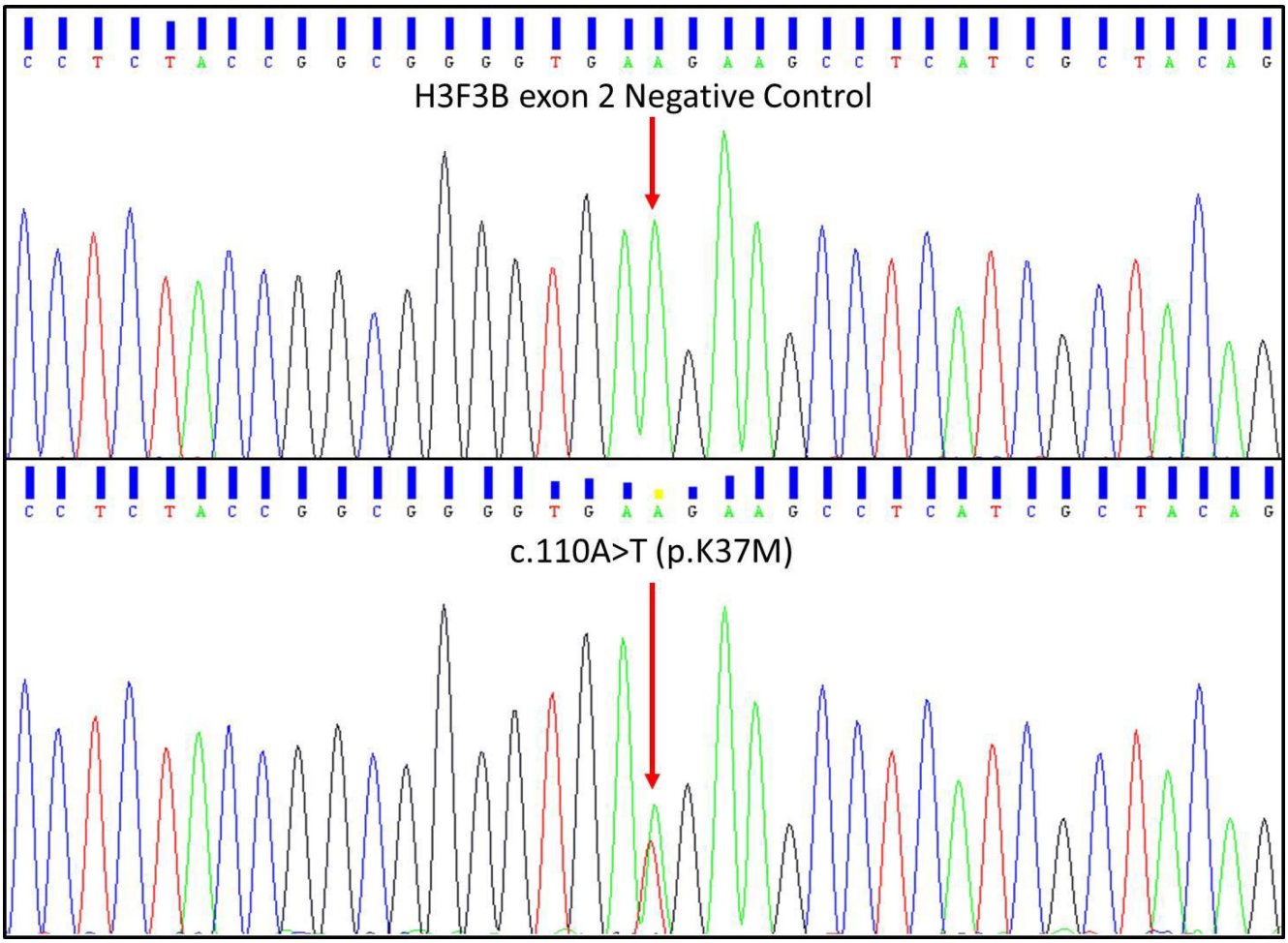


Figure 2. Electropherogram showing the p.Lys36Met mutation in exon 2 of the *H3F3B* gene detected by polymerase chain reaction–based Sanger sequencing.

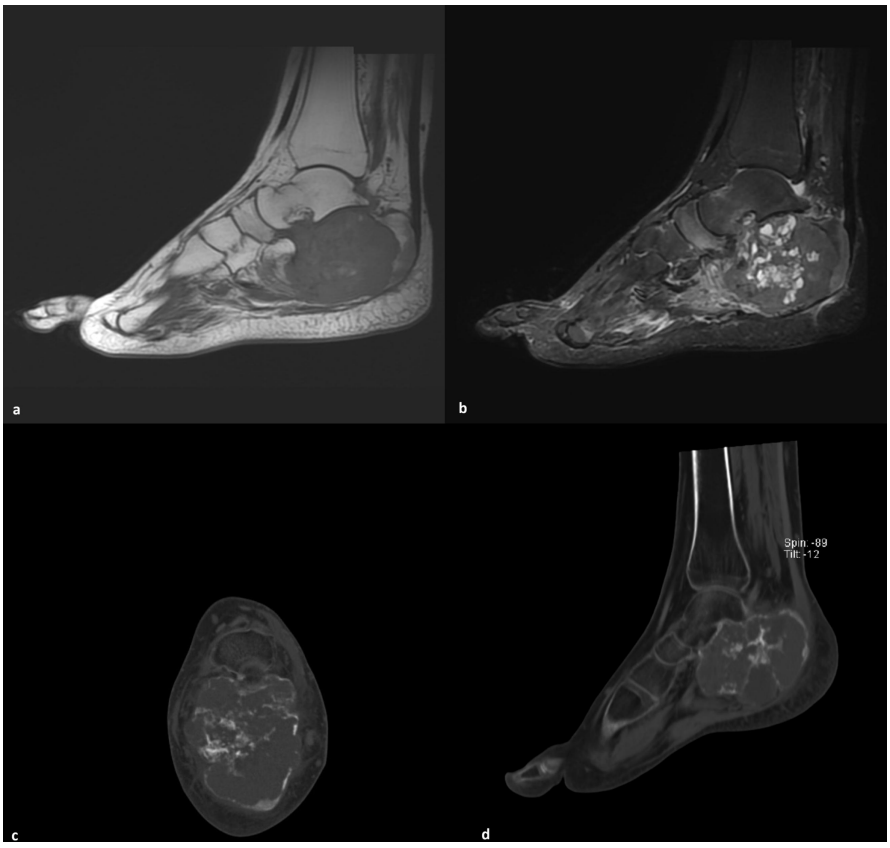


Figure 3. Mass lesion with calcified chondroid matrix content in an expansive appearance completely occupied the calcaneus (96x72x65 mm): a: Magnetic resonance imaging (MRI) T1-weighted sagittal image b: MRI T2-weighted sagittal image c: Computed tomography (CT) axial image d: CT sagittal reformatted image.

is critical for treatment planning; the latter lacks the characteristic *H3F3B* K36M mutation and demonstrates a distinct genomic landscape with different copy number alterations.[22] Clear cell chondrosarcoma, on the other hand, has no specific genetic alterations identified to date.[23] The findings demonstrate that detecting *H3F3B* mutations using PCR-based Sanger sequencing is a valuable molecular tool for diagnosing CB and distinguishing it from these morphologically similar tumors.

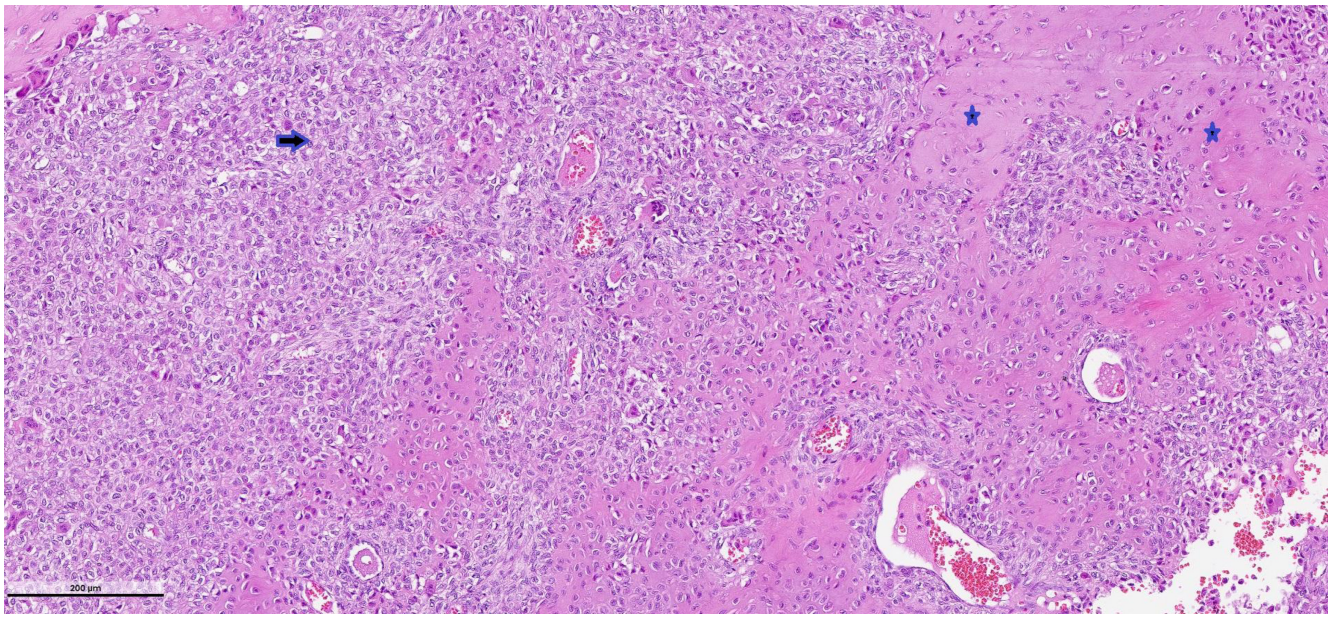


Figure 4. Microscopic appearance of the calcaneal tumor showing polygonal chondroblasts with characteristic nuclear grooves (arrow), multinucleated giant cells, and areas of chondroid matrix formation (asterisks) (H&E, ×20).

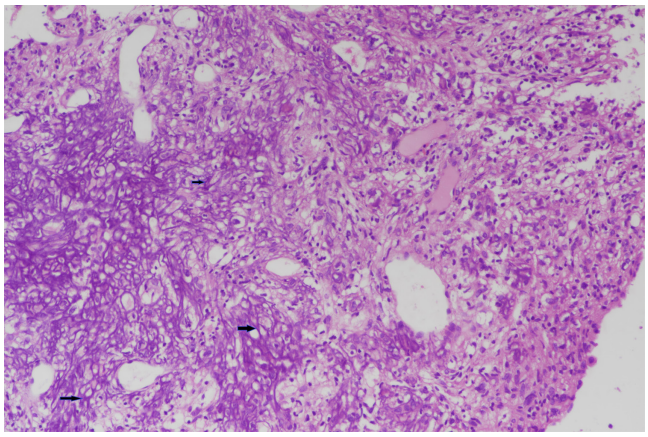


Figure 5. Histopathological features of the mutation-negative tibial tumor exhibiting sheets of polygonal cells with grooved nuclei, scattered multinucleated giant cells, and a characteristic chicken-wire calcification pattern (arrows) (H&E, ×4).

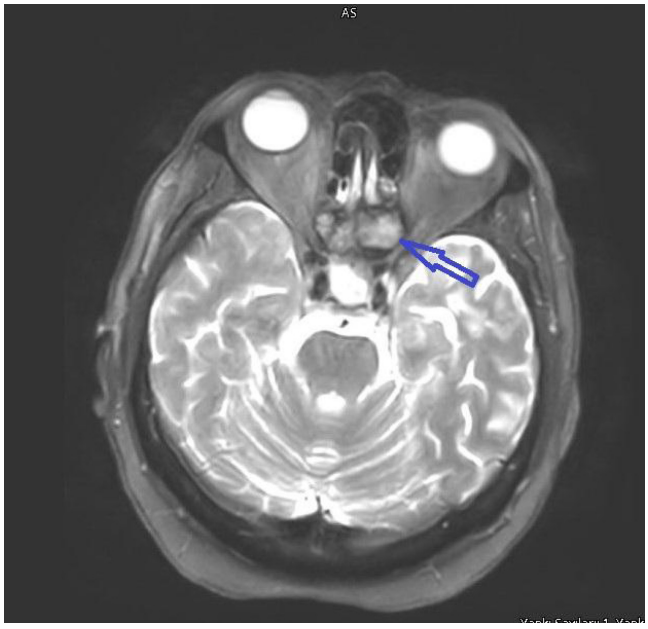


Figure 6. Brain contrast-enhanced magnetic resonance imaging T1-weighted axial sequence of a 72-year-old female demonstrating a well-defined, heterogeneously enhancing lesion extending from the ethmoid bone to the inferior aspect of the frontal lobe (arrow).

Several additional limitations of this study should be acknowledged. First, the retrospective design and multicenter nature of the cohort may have introduced selection bias and inter-institutional variability, particularly in tissue handling, fixation, and decalcification protocols, all of which can directly affect DNA quality and mutation detection rates. Second, although Sanger sequencing is widely accepted, its relatively limited sensitivity compared to more advanced techniques such as next-generation sequencing or digital PCR raises the possibility of false-negative results, especially in samples with low tumor cellularity or significant necrosis. In addition, the targeted nature of the analysis, focusing primarily on hotspot regions, may have limited the detection of rare or non-canonical variants. Third, the lack of complementary immunohistochemical analysis (e.g., H3K36M) or validation using alternative molecular methods limits the ability to cross-confirm the findings. In addition, the absence of a control group comprising histological mimics restricts the assessment of the true diagnostic specificity of *H3F3B* mutations within this cohort. Finally, although clinical and demographic data were available, no formal analysis was performed to explore potential associations between mutation status and clinical outcomes, such as recurrence or tumor behavior, which may represent an area for future investigation. Moreover, the mutation-negative case was not subjected to further molecular or technical validation, and therefore the possibility of a false-negative result or the presence of alternative genetic alterations cannot be excluded.

In conclusion, the findings demonstrate that detecting *H3F3B* mutations using PCR-based Sanger sequencing is an extremely sensitive and valuable molecular tool for diagnosing CB and distinguishing it from morphologically similar tumors. While *H3F3B* mutations are highly prevalent in CB, routine molecular testing may not be strictly necessary for classic cases presenting with typical clinico-radiological and histopathological features. Instead, *H3F3B* mutation testing is most clinically justified and provides the greatest diagnostic benefit in challenging scenarios where conventional histopathological assessment is insufficient. These include cases with equivocal histomorphology, tumors occurring in unusual anatomical locations (e.g., skull base or flat bones), patients outside the typical age range, or when distinguishing CB from malignant mimics, such as CB-like osteosarcoma, is critical for appropriate clinical management.

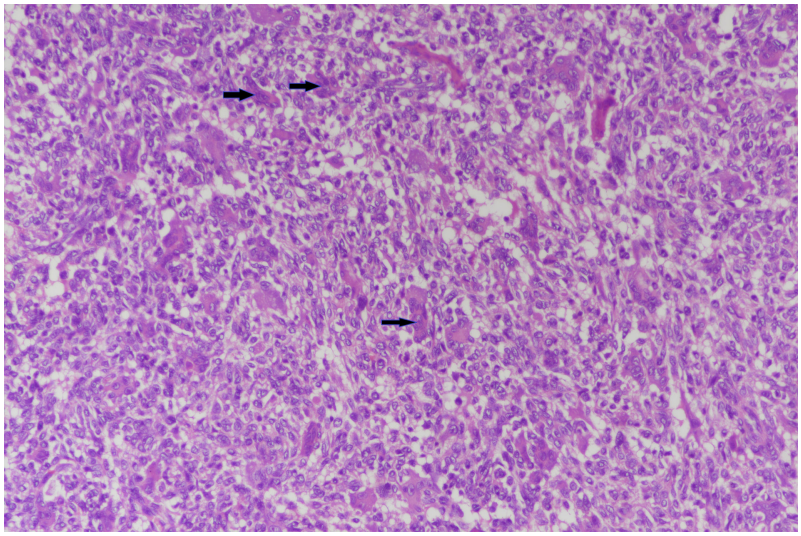


Figure 7. Microscopic examination of the frontal bone tumor revealing tumor cells arranged in sheets with interspersed multinucleated giant cells (arrows) (H&E, ×4).

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ümraniye Training and Research Hospital (Approval no: B.10.1.TKH.4.34.H.GP.0.01/162, Date: May 28, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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