

Should all paediatric osteosarcoma patients be tested for germline TP53 variants? Insights from a single centre sarcoma unit from India

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Abstract

Western studies report germline TP53 pathogenic variants in 5%–10% of paediatric osteosarcoma cases. Data from the Indian subcontinent are lacking. We retrospectively analysed 23 children (≤ 15 years) with osteosarcoma, unselected for personal or family history and treated between January 2020 and July 2025 using next generation sequencing cancer predisposition panels (26-, 84- and 94-gene). No patients had consanguinity or stigmata of syndromic predisposition, and only 17.4% had a family cancer history. Germline TP53 pathogenic/likely pathogenic variants were detected in 13% ($n = 3$). These findings support consideration of germline TP53 testing in paediatric osteosarcoma in low- and middle-income countries wherever feasible, though cost and access barriers remain.

Keywords: *germline variants, osteosarcoma, TP53 mutation, cancer predisposition syndrome, Li-Fraumeni syndrome*

Introduction

Osteogenic sarcoma (OGS), albeit a rarity, constitutes the most prevalent primary bone neoplasm in the paediatric population [1]. Risk factors for osteosarcoma include previous radiotherapy and established cancer predisposition syndromes (CPS), including Li-Fraumeni syndrome (LFS), hereditary retinoblastoma, Diamond-Blackfan anaemia and primary DNA helicase disorders, such as Werner syndrome, Rothmund-Thomson syndrome and Bloom syndrome [2]. Approximately 12% of the individuals with LFS have osteosarcoma, and is one of the sentinel cancers defining the syndrome [3]. In a large cohort of 765 unselected osteosarcoma patients who underwent germline sequencing of TP53 exons, 3.8% and 5.7% were found to carry a known and a rare variant, respectively, of LFS-associated mutation in patients younger than 30 years of age and none in older patients [3]. In children with osteosarcoma, the reported frequency of all pathogenic or likely pathogenic TP53 germline variants in the Western cohorts was around 5%–10% [4–6]. The identification of pathogenic germline variants, especially with the availability of surveillance protocols in many paediatric predisposition syndromes, can have far-reaching implications for the family. Comparable data in children with osteosarcoma from the Indian subcontinent and other low- and middle-income countries (LMICs) are currently lacking. This

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study attempts to identify the same in a small cohort of unselected children diagnosed with osteosarcoma, who were screened for germline cancer predisposition variants in the paediatric cancer genetics clinic (P-CGC).

Methods

Children ≤ 15 years of age with osteosarcoma (upfront or at relapse) diagnosed from January 2020 to July 2025, unselected for family or personal history and was screened for CPS in the P-CGC were retrospectively analysed and formed the study cohort. As genetic testing was not incorporated into routine clinical care during the above study period, most patients diagnosed with osteosarcoma were neither counselled nor tested. Consequently, the present analysis was restricted to the subset of patients who received genetic counselling and subsequently underwent genetic testing. Peripheral blood samples were collected from the patient after pre-test counselling. Information on personal and family history, physical characteristics, tumour type and treatment history that were gathered, along with the pedigree chart created during this process, were reviewed. In the earlier cohort, testing was done using the 26-gene Sophia panel, followed by a 94-gene Illumina panel, and most recently with the 84-gene extended Sophia panel. Post-test counselling included offer of extended family testing and surveillance where required. Pathogenic or likely pathogenic variants in the genes tested in the panel were taken as significant. The required data were collected from electronic medical records and genetics clinic database. The primary objective of the study was to assess the prevalence of germline cancer predisposition variants in paediatric patients diagnosed with osteosarcoma, unselected for family or personal history. The secondary objective was to study the clinical profile of these patients, delineate any family or personal history or physical characteristics suggestive of CPS. Descriptive statistics were used for categorical variables. The prevalence of significant germline variants was expressed as percentage. The study was approved the institutional ethics committee (approval number-OIEC/5147/2026/00001).

Results

A total of 23 patients underwent genetic testing during the study period. The median age at diagnosis was 10 years (IQR: 7–14), and the male-to-female ratio was 0.9:1. Osteoblastic histology predominated (78.3%, $n = 18$), with the remainder classified as chondroblastic (21.7%, $n = 5$). Primary tumours were located in the lower extremity in all but two cases (8.7%), which involved the humerus. Amongst patients with available data, no individual had a history of consanguinity (0/16) or physical stigmata suggestive of a CPS (0/20). A family history of cancer was observed in 17.4% ($n = 4$) of cases, with only one patient (4.3%) exhibiting features specific for LFS.

Pathogenic or likely pathogenic germline variants in TP53, a recognised osteosarcoma predisposition gene, were detected in 13% of patients ($n = 3$). Genetic testing of first-degree relatives in these three patients revealed carrier status amongst the family members tested, including siblings of two patients and the mother of one patient. Two additional likely pathogenic variants were identified in folliculin (FLCN) and MLH1 (8.7%, $n = 2$), though these are not commonly linked to osteosarcoma. Most variants were benign (73.9%, $n = 17$), and one variant was classified as a variant of uncertain significance (VUS) (4.3%, $n = 1$). No documented treatment interruptions or increased toxicities were reported in the patients with CPS. The details are presented in [Table 1](#).

Discussion

The prevalence of pathogenic germline TP53 variants in our cohort (13%) was somewhat higher than that reported in Western cohorts, suggesting possible geographic or population-specific differences [4, 5]. To our knowledge, there are no published data reporting the prevalence of these variants in comparable osteosarcoma cohorts from the Indian subcontinent or other LMICs. Family testing revealed that the variant was present in either a parent or a sibling, suggesting that these variants are likely inherited rather than arising *de novo*, although a family history specifically consistent with LFS was documented in only one of the three cases. This suggests that relying solely on clinical criteria for LFS could miss patients with an underlying predisposition, whether their TP53 variant is inherited or *de novo*. This contrasts with a report from the Children's Oncology Group in an unselected paediatric osteosarcoma cohort, in which nearly half of the pathogenic TP53 germline variants were confirmed to be *de novo* rather than inherited [6]. The germline TP53 variants identified in this study consisted of missense and nonsense mutations, in agreement with previously published findings [7].

Table 1. Details of the patients who had pathogenic, likely pathogenic VUS germline variants.

Age in years, Gender	Histology	Test result	Type of mutation	Family or personal history specific for CPS	Family testing	Predisposition to OGS well established	Status
14, F	Chondroblastic	LP in TP53	Heterozygous missense variant: c.421T>C, p.(Cys141Arg) (Rare variant)	No	Three sisters-TP53 carriers, parents were not tested	Yes	Died of disease progression
14, F	Osteoblastic	P in TP53	Heterozygous nonsense variant: c.916C>T, p.(Arg306) (Rare variant)	No	Brother-TP53 carrier, parents were not tested	Yes	Alive without disease
14, F	Chondroblastic	LP in TP53	Heterozygous missense variant: c.1025G>C, p.(Arg342Pro) (Rare variant)	Yes (Leiomyosarcoma in mother)	Mother-TP53 carrier, father and siblings were not tested	Yes	Alive without disease
6, F	Osteoblastic	LP in MLH1	c.568dup; p.(Ile190AsnfsTer2)	No	Not done	No (but there is a case report of an MLH1 variant in OGS)	Alive without disease
10, M	Osteoblastic	LP in FLCN	Heterozygous splice-donor variant: c.396+1G>T	No	Father-pathogenic variant FLCN carrier	No	Alive without disease
7, F	Osteoblastic	VUS in ATM and RAD51D	-	No	Not done	No	Alive without disease

P-Pathogenic, LP-Likely Pathogenic, VUS-Variant of Uncertain Significance

Two patients in our cohort had likely pathogenic germline variants in MLH1 or FLCN. Although osteosarcoma is not a typical or well-established component of the Lynch syndrome tumour spectrum, sporadic case reports and small series show that it can occur in the context of Lynch syndrome (reported cases mainly with germline MSH2 variants, but one case with an MLH1 germline variant) [8, 9]. But there is no convincing evidence for an inherited predisposition to osteosarcoma associated with germline MLH1 or FLCN variants.

Although the number of paediatric patients tested in this cohort is small, it represents an unselected group and our findings are consistent with prevalence rates reported in western literature. This supports considering universal germline TP53 testing in paediatric osteosarcoma, since the majority of cases did not meet clinical criteria for LFS. Validation in a larger, independent cohort would further confirm these findings. However, implementation in LMICs faces significant challenges, including limited funding, infrastructure and access to genetic services, which constrain the feasibility of extending testing and follow-up to family members. In this context, a targeted TP53 gene testing strategy, which incurs substantially lower costs than multigene panels or whole exome sequencing, may offer a more cost-effective and context-adapted approach in resource-limited settings.

Conclusion

In our unselected cohort of children with osteosarcoma, germline TP53 exonic variants were observed at a notable frequency, suggesting that consideration of targeted germline TP53 testing, may be appropriate for paediatric osteosarcoma patients in LMICs. However, effective implementation in these settings will require strategies to address limitations in access, cost and infrastructure.

List of abbreviations

CPS, Cancer predisposition syndrome; LFS, Li-Fraumeni syndrome; LMIC, Low- and middle-income countries; LP, Likely pathogenic; OGS, Osteosarcoma; P, Pathogenic; VUS, Variant of uncertain significance.

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Conflicts of interest

The authors declare that they have no conflicts of interest

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Nil.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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