HHS Public Access

Author manuscript

Adv Anat Pathol. Author manuscript; available in PMC 2019 August 09.

Published in final edited form as:

Adv Anat Pathol. 2018 July ; 25(4): 217–222. doi:10.1097/PAP.0000000000000190.

Tumor Syndromes Predisposing to Osteosarcoma

Meera Hameed, MD, **Diana Mandelker, MD, PhD**

Memorial Sloan Kettering Cancer Center,NewYork, NY

Abstract

Osteosarcoma is the most common primary bone tumor affecting predominantly adolescents and young adults. It accounts for about 5% of all childhood cancers. While the majority of osteosarcomas are sporadic, a small percentage occur as a component of hereditary cancer syndromes. Early onset, bilateral, multifocal and metachronous tumors suggest genetic predisposition. The inheritance patterns can be autosomal dominant or recessive. These syndromes predispose to a wide variety of mesenchymal and epithelial cancers with propensity for certain mutations being prevalent in specific cancer subtypes. Li-Fraumeni syndrome (LFS), Retinoblastoma (RB), Rothmund-Thompson syndrome (RTS Type 2), Werner Syndrome (WS) and Bloom syndrome (BLM), constitute the majority of the tumor syndromes predisposing to osteosarcoma and will be the focus for this review.

Keywords

Osteosarcoma; hereditary syndromes; cancer predisposition

Introduction

Osteosarcoma (OS) accounts for 1% of all cancer cases in the United States with a bimodal peak of incidence, one occurring in adolescents and the other in the elderly[1]. The majority of the tumors are high grade and as the name implies, production of neoplastic immature osteoid is the “sine qua non” for diagnosis of this malignancy[2]. Prognosis of conventional high grade osteosarcoma without clinically detectable metastases is 70-80% 5-year survival with standard chemotherapy, and drops to 20-40% for those who present with metastatic disease[3,4]. Unlike other childhood sarcomas such as Ewing sarcoma, which are characterized by simple chromosomal rearrangements and low mutation rates, osteosarcoma is a genetically diverse disease with chromosomal copy number changes, structural rearrangements, and mutations[5].While genomic screening over decades with multiple advancing technologies has not pinned down the etiology of osteosarcoma, a higher incidence of OS relative to general population has been consistently found in some cancer predisposition syndromes. These syndromes include Li-Fraumeni Syndrome (TP53), Retinoblastoma (RB1), Rothmund-Thompson Syndrome (RECQL4), Bloom (BLM) and Werner Syndromes (WRN) with individuals inheriting germline inactivating mutations of the respective genes[6–10]. The expression of disease, mutation spectrum and age of onset can

Addres sCorrespondence: Meera Hameed MD, Dept of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, NewYork-NY-10065, hameedm@mskcc.org.

vary even within family and the pattern of inheritance can be autosomal dominant or recessive[11] (Table 1).

Osteosarcoma Predisposing Syndromes:

Hereditary Retinoblastoma: Hereditary retinoblastoma (OMIM# 180200) is a rare autosomal dominant disorder of infancy caused by biallelic mutation of the RB1 gene in developing retinal tissue. Inherited mutation of RB1 in one allele is a predisposing factor for the development of retinoblastoma following the mutation of the second allele[12,13]. In 1971, Dr. Alfred G. Knudson proposed his “two-hit” hypothesis stating that Retinoblastoma is a cancer caused by two mutational events based on his review of 48 hereditary and sporadic cases between 1944-1969 at M.D Anderson Hospital[14]. He proposed that in the inherited form, one mutation is inherited via germ cells and the second one occur in somatic cells, and in the sporadic form both mutations occur in somatic cells (Fig 1). The break-through and genetic proof of his hypothesis came to fruition by the discovery of a missing 13q DNA clone sequence in a Retinoblastoma patient which was later shown to be possess conserved RB1 sequence[15–18]. Retinoblastoma has an incidence of about 1 in 18000 live births and affects all races throughout the world[19]. The RB1 gene has 27 exons and encodes a 928 amino acid Rb protein (pRb). These are composed of two pocket proteins (p107) and (p130) which regulate cell cycle by binding to E2F family of transcription factors[20–22]. Over 1000 different RB germline and somatic mutations have been reported worldwide and the mutations are distributed throughout the gene. Several recurrent and hot spot mutations have been reported and the spectrum of mutations include deletions, nonsense mutations, missense mutations, indels, promoter, splicing mutations and also epigenetic changes such as promoter methylation [23–26] (Fig 2A). In a study by Dommering et al, in a comprehensive cohort of 500 Dutch Rb patients from the Dutch Retinoblastoma Register, more than 180 Rb mutations were found including 33 novel mutations[27]. Mutations included nonsense, frame shift, missense, splice site, large indels, chromosomal deletions and promoter hypermethylation. This study found that the distribution of mutations in this cohort did not differ from that described in worldwide distribution[23]. In the searchable database (RBGMdb) which is based on 932 publications[23] deletions and nonsense mutations were found to be the main inactivating events and nearly 40% of the mutations were recurrent and localize to 16 hot spots with predominance of C to T conversions and the reminder of mutations were scattered along the gene. Genotype-phenotype correlations, mechanisms linking mutations to ethnicity, delayed onset and low penetrance could be ascertained from this study. The contribution of mutation types to secondary malignancies is not well known.

Some patients with sporadic retinoblastoma cases may carry a mosaic RB1 mutation[28], and detecting these low-level variants is important for screening and for family planning purposes. Additionally, individuals who present with retinoblastoma and a detected pathogenic RB1 germline variant may either be a “de novo” case, or one parent may be a germline mosaic for the variant. In the latter case, there is a substantial risk of other children of this parent developing retinoblastoma.

Osteosarcoma Association: While the children with hereditary retinoblastoma have excellent survival, they are at increased risk for developing bone and soft tissue sarcomas,

most notably osteosarcoma[29,30]. This risk is attributed to genetic factors, radiation therapy and chemotherapy, with radiation therapy carrying the highest risk[30–33]. While a 69-fold increase in the development of osteosarcoma has been reported, this can dramatically rise to 400-fold after radiation exposure, compared to population rates[32]. The age incidence is similar to sporadic osteosarcoma (adolescents and young adults) and the most common site of location is within the radiation field, however tumors also occur outside the radiation field such as lower extremities[30,31,34,35]. Kleinerman RA et al reported the location of osteosarcomas included skull and face (61%), lower limbs (29%), trunk (7%) and unknown locations (3.8%) in 75 patients with hereditary retinoblastoma following radiation[30]. In a retrospective review of skull-based malignancies in hereditary retinoblastoma survivors at Memorial Sloan Kettering Cancer Center, osteosarcomas accounted for 39% of the tumors[36]. The incidence of somatic RB1 mutation in sporadic osteosarcoma ranges between 30-75% [37].

Imaging and Pathology: Radiological findings are similar to conventional sporadic osteosarcoma. Lesions are destructive, ill defined, mixed lytic and sclerotic with wide transition zone and extend beyond cortex with soft tissue mass and calcifications (Fig 2). Pathological features are often typical with production of neoplastic osteoid and morphology showing osteoblastic, chondroblastic, MFH-like or telangiectatic features (Fig 3).

Li-Fraumeni Syndrome (LFS)

Described in 1969 by Drs. Frederick Li and Joseph F. Fraumeni Jr, this hereditary cancer predisposition syndrome is associated with sarcomas, breast carcinoma, brain tumors, leukemias and adrenocortical carcinomas[2]. LFS (OMIM #151623) is an autosomal dominant disorder and is characterized by germline mutations in TP53 gene[3,4]. Classic Li-Fraumeni criteria include proband diagnosed with sarcoma before age 45, has first –degree relative with any cancer before age 45 and another first or second degree relative with any cancer before age 45 or sarcoma at any age[2]. LFS is associated with an extremely high lifetime risk of cancer. The risk of cancer has been estimated to be 50% by 30 years of age and 90% by age 60 years [38], and the relative risk of osteosarcoma has been estimated at 107 [39]. Pathogenic germline variants in TP53 result in protein loss of function. While nonsense, frameshift and splicing variants can span the gene sequence, many of the pathogenic missense variants in TP53 occur within the DNA binding domain (DBD)[5,6]

LFS has been detected in approximately 5% of osteosarcoma cases under the age of 30, and osteosarcoma is the most common sarcoma found in individuals with LFS [7]. The same study found no cases of Li-Fraumeni syndrome in osteosarcoma patients with onset >30 years of age [7]. Moreover, osteosarcoma is diagnosed in approximately 12% of individuals with LFS [40]. Since osteosarcoma is relatively common in LFS families and the age of onset is early, it may be the first presenting neoplasm in a family suggestive of LFS. For example, the family presented in figure 4 was brought to clinical attention when the proband was diagnosed with osteosarcoma at age 19. His 56 year old father was then diagnosed with leiomyosarcoma, melanoma, and an adrenocortical neoplasm and both tested positive for Li Fraumeni syndrome. Other than a typically younger age of onset, the presentation of osteosarcoma in LFS patients is similar to sporadic osteosarcoma with metaphysis of long bones as the most

commonly affected site [8]. Histological features are similar to conventional osteosarcomas and the tumor is composed of pleomorphic tumor cells containing variable amounts of osteoid matrix and can be sub-typed as osteoblastic, chondroblastic and fibroblastic types depending on the predominant matrix produced by the tumor [2]

Families with LFS often show genetic anticipation, with earlier onset of cancers in successive generations. This phenomenon may be attributed to telomere shortening[41,42]. The most common TP53 mutations in sarcoma patients of LFS are missense mutations (72.8%) and involve codons 273,248,282,175 and 220 in the DNA binding domain (DBD)[8]. High prevalence of codon 245 and 282 were seen in osteosarcoma whereas more than 20% of all mutations are seen at codon 273 in patients with rhabdomyosarcoma[8]. Mutations outside the DBD (codons 337 or 344) are associated with leiomyosarcoma and unlike osteosarcoma and rhabdomyosarcoma, frameshift, splice –site and nonsense mutation are more frequent. It is postulated that mutations predicting absence of wild type protein lead to late-onset type sarcoma and missense DBD mutations accumulating mutant proteins give rise to early onset types of sarcoma such as osteosarcoma and rhabdomyosarcoma[8].For those with a known germline mutation in TP53, recommended screening includes whole body MRI to screen for sarcomas and other cancers [43].

Werner Syndrome:

Werner Syndrome, an autosomal recessive disorder (OMIM#27770), also known as adult progeria is characterized by premature aging, bilateral cataracts, osteoporosis, short –stature and scleroderma –like skin changes[44]. Founder effect contributes to the high frequency seen in Japan[45]. Werner Syndrome is caused by mutations of the WRN gene, which is a RecQ helicase, located on chromosome 8p11.1 [46]. Patients with Werner Syndrome are susceptible to multiple cancers including osteosarcoma, soft tissue sarcoma, meningioma, myeloid disorders, melanomas, thyroid carcinoma, hematological malignancies and other epithelial cancers[44]. The WRN gene is the only RecQ helicase with a 3’-5’ exonuclease activity. More than 90 mutations have been identified and they are all inactivating and include base substitutions, insertions, deletions and complex mutations, which disrupt the WRN, open reading frame [47]. WRN gene is composed of 35 exons that encode a 1432 amino acid protein which contains RecQ-type helicase domains in central region and an exonuclease domain in N-terminal region. There are two consensus regions, RecQ helicase conserved region (RQC), the helicase RNaseD C-terminal conserved region (HRDC), which are present between the helicase and nuclear localization signal[47]. Osteosarcomas occur at a later age in these patients (ages ranging from 35-57) and tend to present at atypical sites such as foot, ankle, patella in contrast to more common sites such as long bones[48]. An association of WRN SNP 1367R with bone and soft tissue sarcomas has been reported in Werner Syndrome with R allele having a protective effect[49].

Rothmund –Thompson Syndrome (RTS)

Rothmund-Thompson syndrome (OMIM #268400) is an autosomal recessive disorder caused by biallelic germline mutations in RECQL4, and is strongly associated with osteosarcoma predisposition[21]. The syndrome usually presents with a characteristic rash in

infancy and is also characterized by poikiloderma, sparse hair, frontal bossing, saddle nose, short stature, radial defects, hypoplastic patellae, esophageal or pyloric atresia, annular pancreas, myelodysplasia and cataracts[21]. Pathogenic mutations in RECQL4 are loss of function mutations and include nonsense, frameshift, splice site and intronic deletions[23]. Unlike other TP53 and RB mutated syndromes, RECQL4 mutations are not seen in sporadic OS, and present in the context of Rothmund-Thompson syndrome[23]. In a review of 61 patients with RTS by Stinco et al[24], OS accounted for 62% of cancers, of which 3 were multicentric (metachronous) and 12 developed before the age of ten. Another cohort of 41 RTS patients found that 32% of patients developed osteosarcoma, though 22/41 (54%) of patients in this study were under the age of 15, so the incidence of osteosarcoma in RTS may be higher[50]. An association of gene truncation mutations with development of OS has been proposed by some authors[25]. Histological subtypes described are similar to conventional OS and multimodality chemotherapy has been recommended as treatment of choice[26] based on outcome on a series of 7 patients. A second syndrome caused by RECQL4 mutations and predisposition to OS is RAPADILINO syndrome[21]. The name is the acronym for: RA: Radial dysplasia; PA: Patella aplasia or hypoplasia and left high arched palate; DI: Diarrhea and Dislocated joints; LI: Little size and Limb malformations; NO: long, slender Nose and NOrmal Intelligence)[21]. Most individuals with RAPADILINO syndrome carry a specific founder mutation, RECQL4 c.1390+2delT, and also have an increased risk of osteosarcomas and lymphomas[51].

Bloom Syndrome (BLM):

Bloom Syndrome (OMIM#210900) is an autosomal recessive disease characterized by short stature, sun sensitive rash and sparse subcutaneous fat and is caused by mutations in BLM gene, which is a RecQ helicase[52]. While majority of the cancers in BLM are carcinomas, leukemias and lymphomas, the osteosarcoma rate is higher than general population[53]. The prevalence rate in Ashkenazi Jews is 1% and susceptible individuals can be offered genetic testing[54].

Summary

In syndromes predisposing to osteosarcoma, tumor presentation can be the first manifestation and presenting diagnosis. This possibility should be considered especially in cases with unusual presentation and family history of other cancers. The rarity of these syndromes is a challenge and a high index of suspicion is needed to pursue genetic counseling and further testing to detect underlying heritable mutations. Through next generation sequencing technology we have learned that there is a higher than expected prevalence of hereditary cancer predisposition syndromes in advanced cancer patients. In a recent study of 1040 patients with advanced cancers, germline sequencing of a broad panel of cancer related genes showed 17.5% of the individuals had clinically actionable heritable mutations, and over half of these mutations would not have been detected using clinical guidelines alone[55]. In rare cancers such as osteosarcoma which affects young individuals, early recognition of patients with predisposition syndromes allows for genetic testing of at-risk family members, better surveillance and possible targeted treatment options.

References

1. Mirabello L, Troisi RJ, Savage SA. International osteosarcoma incidence patterns in children and adolescents, middle ages and elderly persons. Int J Cancer. 2009;125:229–234. [PubMed: 19330840]
2. Fletcher C, Bridge JA, Hogendoorn PC, et al. WHO Classification of Tumours of Soft Tissue and Bone. 4th Edition: 281–295.: IARC: Lyon; 2013.
3. Moore DD, Luu HH. Osteosarcoma. Cancer Treat Res. 2014;162:65–92. [PubMed: 25070231]
4. Briccoli A, Rocca M, Salone M, et al. High grade osteosarcoma of the extremities metastatic to the lung: long-term results in 323 patients treated combining surgery and chemotherapy, 1985-2005. Surg Oncol. 2010;19:193–199. [PubMed: 19515554]
5. Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. Sarcoma. 2011;2011:548151. [PubMed: 21437228]
6. Fuchs B, Pritchard DJ. Etiology of osteosarcoma. Clin Orthop Relat Res. 2002:40–52.
7. Hansen MF, Koufos A, Gallie BL, et al. Osteosarcoma and retinoblastoma: a shared chromosomal mechanism revealing recessive predisposition. Proc Natl Acad Sci U S A. 1985;82:6216–6220. [PubMed: 2994066]
8. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990;250:1233–1238. [PubMed: 1978757]
9. Wang LL, Gannavarapu A, Kozinetz CA, et al. Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. J Natl Cancer Inst. 2003;95:669–674. [PubMed: 12734318]
10. Mohaghegh P, Hickson ID. DNA helicase deficiencies associated with cancer predisposition and premature ageing disorders. Hum Mol Genet. 2001;10:741–746. [PubMed: 11257107]
11. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005;23:276–292. [PubMed: 15637391]
12. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70. [PubMed: 10647931]
13. Knudson AG. Two genetic hits (more or less) to cancer. Nat Rev Cancer. 2001;1:157–162. [PubMed: 11905807]
14. Knudson AG Jr Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971;68:820–823. [PubMed: 5279523]
15. Dryja TP, Rapaport JM, Joyce JM, et al. Molecular detection of deletions involving band q14 of chromosome 13 in retinoblastomas. Proc Natl Acad Sci U S A. 1986;83:7391–7394. [PubMed: 2876425]
16. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature. 1986;323:643–646. [PubMed: 2877398]
17. Lee WH, Bookstein R, Hong F, et al. Human retinoblastoma susceptibility gene: cloning, identification, and sequence. Science. 1987;235:1394–1399. [PubMed: 3823889]
18. Fung YK, Murphree AL, T'Ang A, et al. Structural evidence for the authenticity of the human retinoblastoma gene. Science. 1987;236:1657–1661. [PubMed: 2885916]
19. Kivela T The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol. 2009;93:1129–1131. [PubMed: 19704035]
20. Chellappan SP, Hiebert S, Mudryj M, et al. The E2F transcription factor is a cellular target for the RB protein. Cell. 1991;65:1053–1061. [PubMed: 1828392]
21. Cobrinik D, Whyte P, Peeper DS, et al. Cell cycle-specific association of E2F with the p130 E1A-binding protein. Genes Dev. 1993;7:2392–2404. [PubMed: 8253385]
22. Zamanian M, La Thangue NB. Transcriptional repression by the Rb-related protein p107. Mol Biol Cell. 1993;4:389–396. [PubMed: 7685208]
23. Valverde JR, Alonso J, Palacios I, et al. RB1 gene mutation up-date, a meta-analysis based on 932 reported mutations available in a searchable database. BMC Genet. 2005;6:53. [PubMed: 16269091]
24. Price EA, Price K, Kolkiewicz K, et al. Spectrum of RB1 mutations identified in 403 retinoblastoma patients. J Med Genet. 2014;51:208–214. [PubMed: 24225018]

25. Harbour JW. Overview of RB gene mutations in patients with retinoblastoma. Implications for clinical genetic screening. Ophthalmology. 1998;105:1442–1447. [PubMed: 9709755]
26. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. Nat Rev Dis Primers. 2015;1:15021. [PubMed: 27189421]
27. Dommering CJ, Mol BM, Moll AC, et al. RB1 mutation spectrum in a comprehensive nationwide cohort of retinoblastoma patients. J Med Genet. 2014;51:366–374. [PubMed: 24688104]
28. Chen Z, Moran K, Richards-Yutz J, et al. Enhanced sensitivity for detection of low-level germline mosaic RB1 mutations in sporadic retinoblastoma cases using deep semiconductor sequencing. Hum Mutat. 2014;35:384–391. [PubMed: 24282159]
29. Marees T, Moll AC, Imhof SM, et al. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. J Natl Cancer Inst. 2008;100:1771–1779. [PubMed: 19066271]
30. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol. 2005;23:2272–2279. [PubMed: 15800318]
31. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. Br J Cancer. 1986;53:661–671. [PubMed: 3718823]
32. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA. 1997;278:1262–1267. [PubMed: 9333268]
33. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. J Natl Cancer Inst. 2009;101:581–591. [PubMed: 19351917]
34. Woo KI, Harbour JW. Review of 676 second primary tumors in patients with retinoblastoma: association between age at onset and tumor type. Arch Ophthalmol. 2010;128:865–870. [PubMed: 20625047]
35. Hawkins MM, Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. J Natl Cancer Inst. 1996;88:270–278. [PubMed: 8614005]
36. Liu JC, Givi B, Wolden S, et al. Secondary skull base malignancies in survivors of retinoblastoma: the memorial sloan kettering cancer center experience. Skull Base. 2011;21:103–108. [PubMed: 22451810]
37. Ottaviani G, Jaffe N. The etiology of osteosarcoma. Cancer Treat Res. 2009;152:15–32. [PubMed: 20213384]
38. Lustbader ED, Williams WR, Bondy ML, et al. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet. 1992;51:344–356. [PubMed: 1642235]
39. Ruijs MW, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet. 2010;47:421–428. [PubMed: 20522432]
40. Ognjanovic S, Olivier M, Bergemann TL, et al. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. Cancer. 2012;118:1387–1396. [PubMed: 21837677]
41. Tabori U, Nanda S, Druker H, et al. Younger age of cancer initiation is associated with shorter telomere length in Li-Fraumeni syndrome. Cancer Res. 2007;67:1415–1418. [PubMed: 17308077]
42. Bougeard G, Brugieres L, Chompret A, et al. Screening for TP53 rearrangements in families with the Li-Fraumeni syndrome reveals a complete deletion of the TP53 gene. Oncogene. 2003;22:840–846. [PubMed: 12584563]
43. Kratz CP, Achatz MI, Brugieres L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res. 2017;23:e38–e45. [PubMed: 28572266]
44. Goto M, Miller RW, Ishikawa Y, et al. Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev. 1996;5:239–246. [PubMed: 8722214]
45. Goto M, Tanimoto K, Horiuchi Y, et al. Family analysis of Werner's syndrome: a survey of 42 Japanese families with a review of the literature. Clin Genet. 1981;19:8–15. [PubMed: 7460386]
46. Calvert GT, Randall RL, Jones KB, et al. At-risk populations for osteosarcoma: the syndromes and beyond. Sarcoma. 2012;2012:152382. [PubMed: 22550413]
47. Lebel M, Monnat RJ Jr Werner syndrome (WRN) gene variants and their association with altered function and age-associated diseases. Ageing Res Rev. 2017;41:82–97. [PubMed: 29146545]

48. Ishikawa Y, Miller RW, Machinami R, et al. Atypical osteosarcomas in Werner Syndrome (adult progeria). Jpn J Cancer Res. 2000;91:1345–1349. [PubMed: 11123436]

49. Nakayama R, Sato Y, Masutani M, et al. Association of a missense single nucleotide polymorphism, Cys1367Arg of the WRN gene, with the risk of bone and soft tissue sarcomas in Japan. Cancer Sci. 2008;99:333–339. [PubMed: 18271933]

50. Wang LL, Levy ML, Lewis RA, et al. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am J Med Genet. 2001;102:11–17. [PubMed: 11471165]

51. Siitonen HA, Sotkasiira J, Biervliet M, et al. The mutation spectrum in RECQL4 diseases. Eur J Hum Genet. 2009;17:151–158. [PubMed: 18716613]

52. Ellis NA, Groden J, Ye TZ, et al. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell. 1995;83:655–666. [PubMed: 7585968]

53. German J Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet. 1997;93:100–106. [PubMed: 9062585]

54. Li L, Eng C, Desnick RJ, et al. Carrier frequency of the Bloom syndrome blmAsh mutation in the Ashkenazi Jewish population. Mol Genet Metab. 1998;64:286–290. [PubMed: 9758720]

55. Mandelker D, Zhang L, Kemel Y, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA. 2017;318:825–835. [PubMed: 28873162]

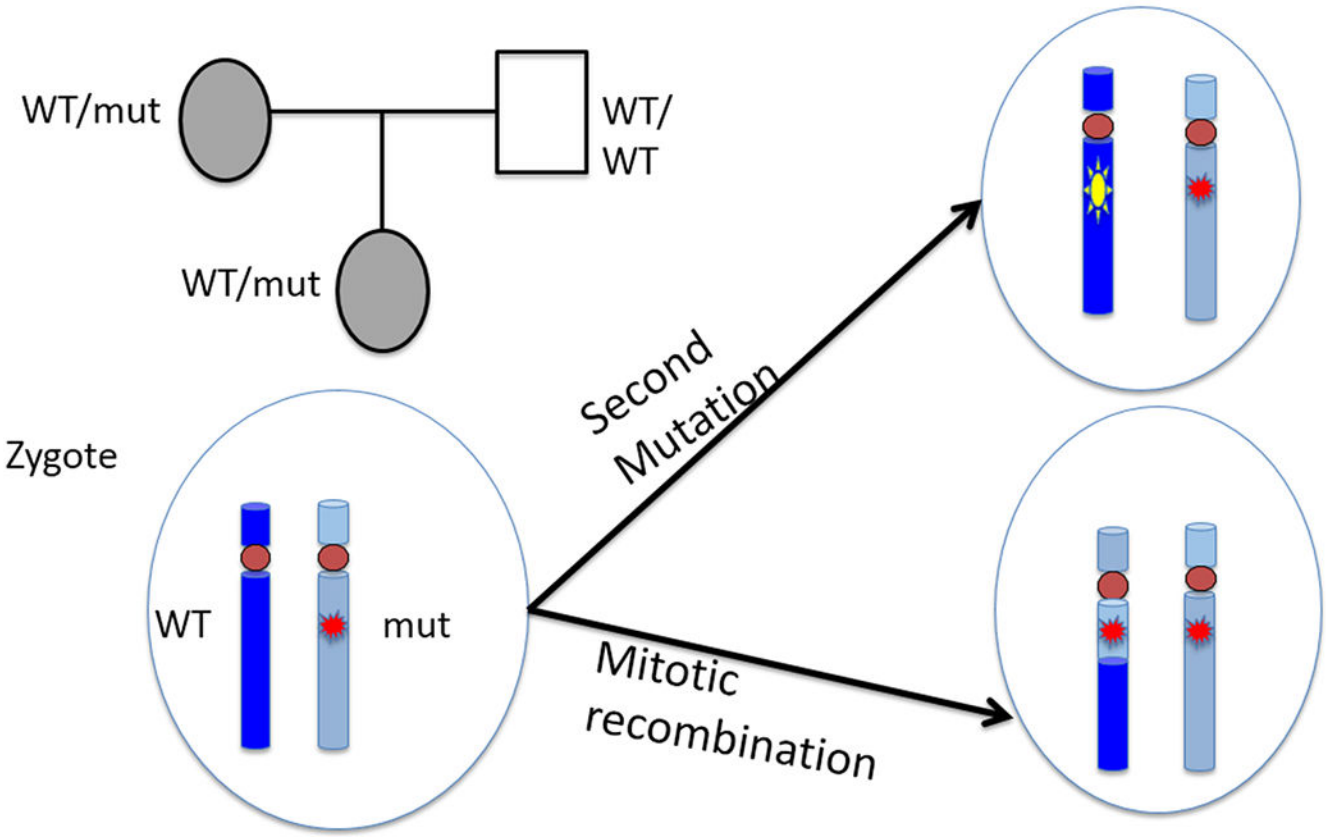

Fig 1:

Schematic Diagram of “Two-Hit” Hypothesis- One mutation is inherited through germline followed by second mutation or mitotic recombination in somatic cells

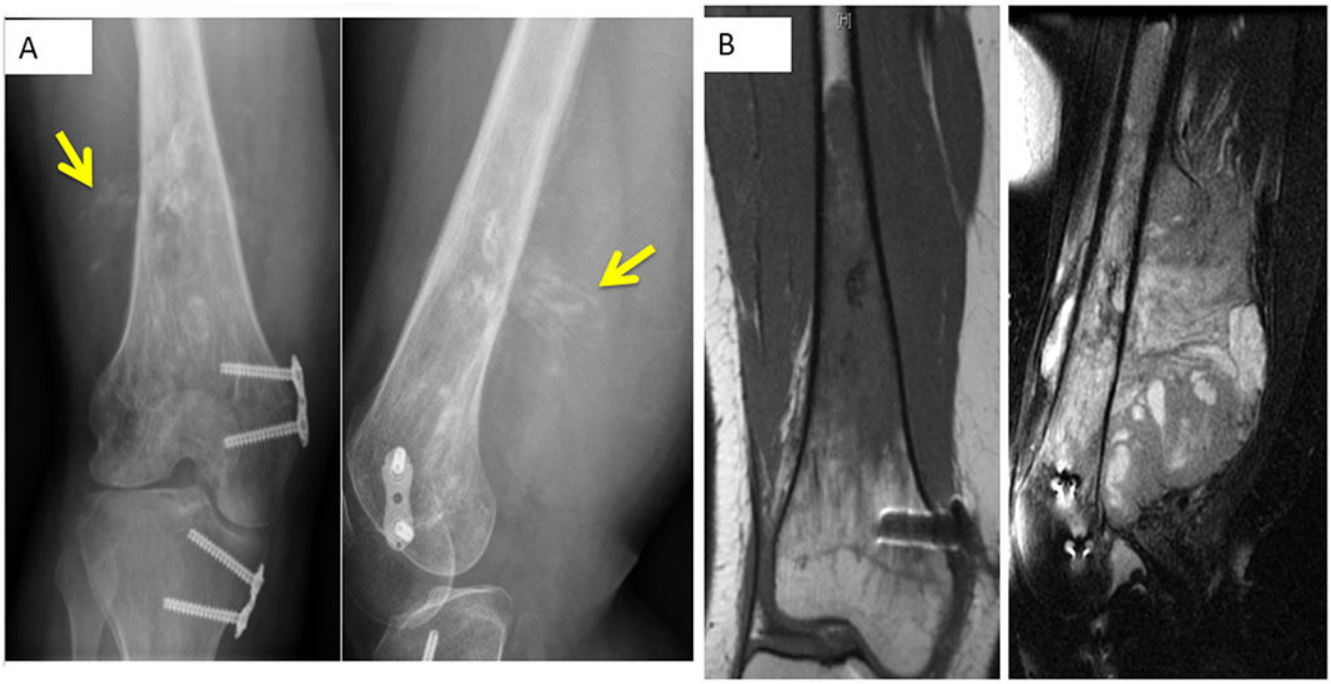

Fig 2 A and B:

A. Plain radiograph showing mixed lytic and sclerotic lesion in distal femoral metadiaphysis with multiple soft tissue calcifications (arrows). B. MR TW and T2W FS images showing distal femoral marrow lesion with a large soft tissue mass (Courtesy: Dr. Sinchun Hwang-MSKCC)

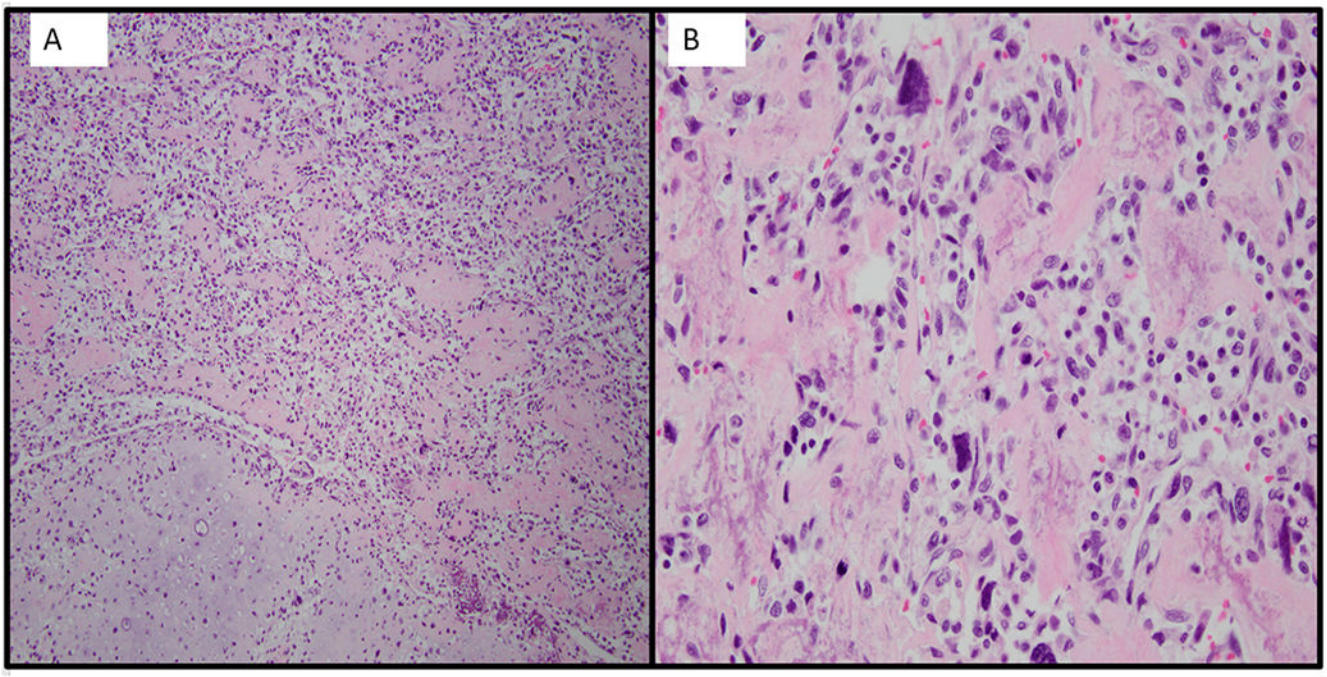

Fig 3 A and B:

A. Photomicrograph of osteosarcoma showing broad islands of osteoid matrix surrounded by tumor cells with an adjacent chondroid component (200X). B. High power view of osteoid matrix showing irregular mineralization surrounded by osteoblasts and pleomorphic tumor cells (400X)

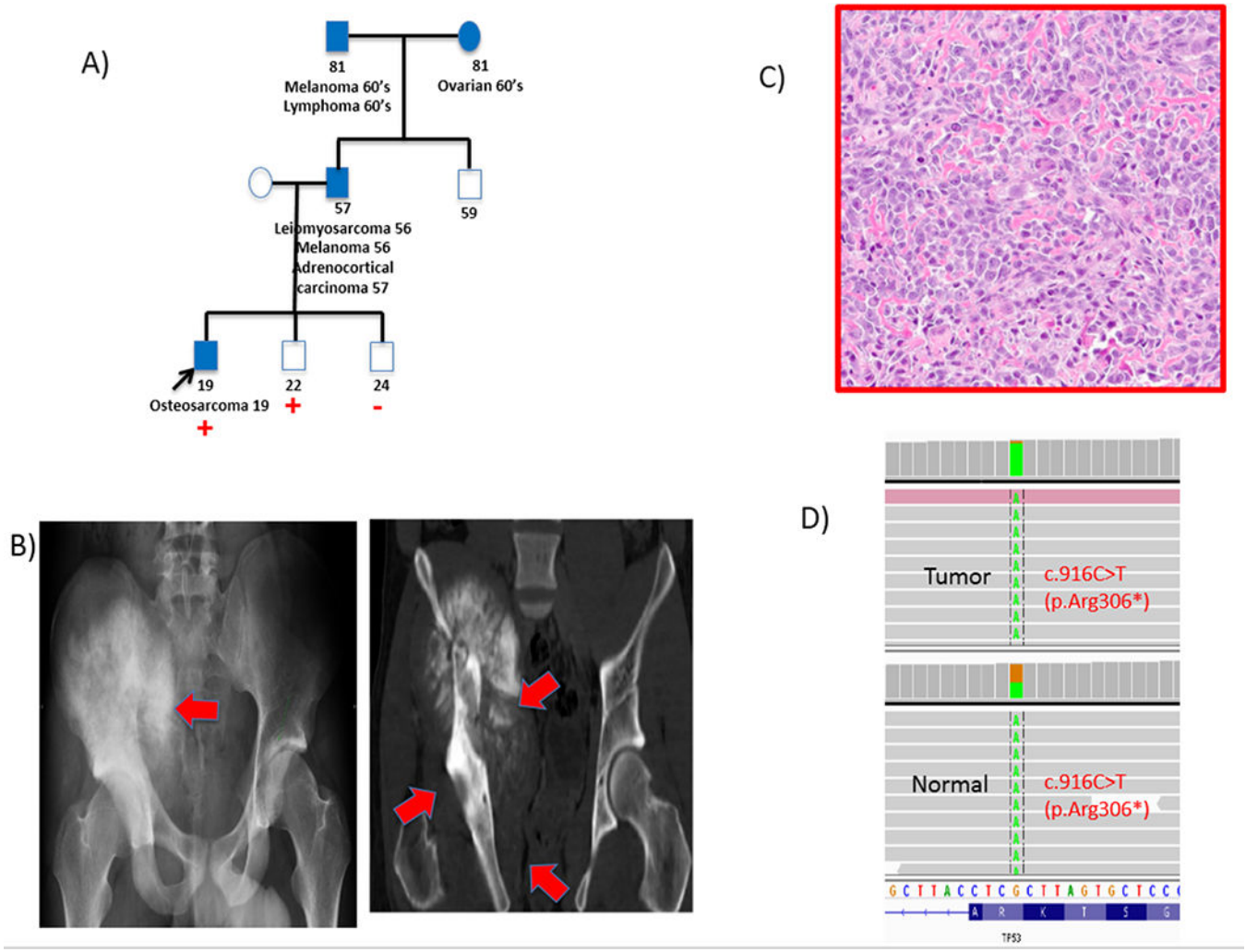

Fig 4 A-D:

A. Pedigree of LFS family. B. Plain radiograph showing a large densely calcified mass in right iliac bone and acetabulum with extraosseous mass and poorly defined periosteal reaction (arrow) Coronal CT scan Coronal CT shows a right iliac lesion with mixed lytic and sclerotic components extending to the right ilium and acetabulum with extensive periosteal reaction (arrows) (Courtesy: Dr.Sinchun Hwang-MSKCC). C. Photomicrograph of the tumor showing lace –like pink osteoid surrounded by osteoblastic tumor cells (400X). D. Next generation sequencing analysis of DNA extracted from tumor and peripheral blood of proband -IGV genome browser screenshot showing a TP53 c.916 C>T (p.Arg306*)exon 8 mutation seen in both tumor sample and normal (peripheral blood).

Table 1:

Osteosarcoma Predisposition Syndromes

Predisposition Syndrome	Inheritance Pattern	Gene	Chromosome	Tumor Types
Li-Fraumeni	AD	TP53	17p13.1	Osteosarcoma, Soft Tissue sarcoma, Breast Cancer, Leukemia, Adrenocortical Carcinoma, Brain Tumors
Retinoblastoma	AD	RB1	13q14.2	Osteosarcoma, soft tissue sarcoma, melanoma
Rothmund Thompson	AR	RECQL4	8q24.3	Osteosarcoma, squamous and basal cell carcinoma
Werner	AR	WRN	8p12	Osteosarcoma, soft tissue sarcoma, Melanoma, Myeloid, Thyroid cancer, other epithelial cancers
Bloom	AR	BLM	15q26.1	Carcinomas, Lymphomas, leukemias, osteosarcoma

AD:Autosomal Dominant; AR:Autosomal Recessive