Tumor Syndromes That Include Bone Tumors
An Update

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KEYWORDS

• Tumor syndromes • Bone neoplasms • Bone cancer • Osteosarcoma
• Genetic syndromes with bone cancer predisposition

Key points

- Tumor syndromes, which include bone neoplasias, are genetic predisposing conditions characterized by the development of a pattern of malignancies with early onset within a family.
- Occurrence of bilateral, multifocal, or metachronous neoplasias and specific histopathologic findings can suggest a genetic predisposition syndrome. Moreover, additional clinical features not related to the neoplasia can be an hallmark of specific genetic syndromes.
- Mostly, those diseases have an autosomal dominant pattern of inheritance with variable percentage of penetrance.
- On the other hand, some syndromic disorders with an increased tumor risk may show an autosomal recessive transmission or are related to somatic mosaicism.
- To date many genetic tumor syndromes are known. This update is specifically focused on syndromes predisposing to osteosarcoma (OS) (Li-Fraumeni syndrome [LFS], retinoblastoma [Rb], Rothmund-Thomson syndrome [RTS], and Werner syndrome [WS]) and to chondrosarcoma (multiple osteochondromas [MO] and enchondromatosis).

ABSTRACT

Tumor syndromes, including bone neoplasias, are genetic predisposing conditions characterized by the development of a pattern of malignancies within a family at an early age of onset. Occurrence of bilateral, multifocal, or metachronous neoplasias and specific histopathologic findings suggest a genetic predisposition syndrome. Additional clinical features not related to the neoplasia can be a hallmark of specific genetic syndromes. Mostly, those diseases have an autosomal dominant pattern of inheritance with variable percentage of penetrance. Some syndromic disorders with an increased tumor risk may show an autosomal recessive transmission or are related to somatic mosaicism. Many genetic tumor syndromes are known. This update is specifically focused on syndromes predisposing to osteosarcoma and chondrosarcoma.

OVERVIEW

Tumor syndromes are genetic conditions predisposing to developing malignancies, including a single primary tumor or multicentric neoplasms, with an early age of onset.[1]

Disclosure Statement: The authors have nothing to disclose.
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Surgical Pathology 10 (2017) 749–764
http://dx.doi.org/10.1016/j.path.2017.04.009

It is well known that genetic alterations play a major role in cancer pathogenesis[2,3] and approximately 5% to 10% of all cancers arise from a background of genetic predisposition.[1] A suggestion of a genetic predisposition syndrome is given by onset of a certain cancer type at an earlier age than in the general population; occurrence of bilateral, multifocal, or metachronous neoplasias; specific histopathologic findings. Moreover, additional clinical features not related to the neoplasia can be a hallmark of specific genetic syndromes.[4] In a majority of cases, those diseases have an autosomal dominant pattern of inheritance with a complete or incomplete penetrance.[1]

Clinical expression – number or type of neoplasias and age of onset – can be extremely variable within the same family.[1] On the other hand, some syndromic disorders with an increased tumor risk, like Rothmund-Thomson syndrome (RTS) or Werner Syndrome (WS), may be inherited in an autosomal recessive way.[5–7] In addition, nonhereditary somatic mosaicism has been described for polyostotic fibrous dysplasia and McCune-Albright syndrome and for enchondromatosis (Ollier disease [OD] and Maffucci syndrome [MS]).[7]

So far, many genetic tumor syndromes are known.[1] This review focuses on tumor syndromes that include OS (**Table 1**) and chondrosarcoma (**Table 2**).

TUMOR SYNDROMES AND OSTEOSARCOMA

OS is the most common primary bone tumor, histologically characterized by the presence of malignant mesenchymal cells and the production of osteoid[8]; multiple somatic mutations and chromosomal aberrations have been described in sporadic OS.[9] Some hereditary genetic syndromes confer genetic predisposition to developing OS (see **Table 1**).

LI-FRAUMENI SYNDROME

LFS (Online Mendelian Inheritance in Man [OMIM] #151623), is an autosomal dominant cancer predisposition syndrome, resulting from germline heterozygous mutations of the tumor suppressor gene *TP53* located on chromosome 17p13.1 (OMIM*191170).[7,10]

Tp53 gene product, the tumor protein p53, plays an important role in determining the fate of cells with damaged DNA, delaying cell cycle progression, and addressing DNA repair or apoptosis. When the wild-type p53 protein is absent, cells containing damaged DNA can survive and proliferate, contributing to malignant transformation.[11]

Therefore, the involvement of the p53 protein becomes a determinant aspect when considering the wide tumor spectrum in LFS. Its high variability regarding age of onset and cancer types between individuals, even within the same family, makes it difficult to suggest surveillance for early diagnosis and to have a full understanding of pathogenic mechanism involved in cancer development.[12] Since its first description in 1969 by Frederick Li and Joseph Fraumeni, the classic clinical definition of LFS was first established almost 20 years later.[12] The tumor spectrum was subsequently widened in 1988 and these malignancies still represent the majority of LFS-related tumors (**Box 1**).[12] Over time, more patients were described sharing only some of the characteristics previously identified; then, new sets of criteria for clinical diagnosis and for selecting patients for genetic testing were added. The Chompret criteria, developed in 2001 from a French cohort of *TP53* mutation carriers showed the highest predictive value[13] and its more recent version (Bougeard and colleagues[12]) had an estimated sensitivity of 82% to 95% and specificity of 47% to 58%. **Fig. 1** summarizes the different diagnostic criteria for LFS.

Table 1
Main genetic syndromic conditions associated with osteosarcoma

Disease	Main Cancer Types	Bone Cancer Type	Gene	Transmission
LFS OMIM #151623	Breast cancer, soft tissue sarcoma, OS, CNS tumor, ACC, leukemia, bronchoalveolar lung cancer	OS	*TP53*	AD
RTS OMIM #268400	OS; skin cancer	OS	*RECQL4*	AR
Rb OMIM #180200	Retinoblastoma, retinoma, pinealoblastoma	OS	*RB1*	AD
WS OMIM #277700	Thyroid neoplasms, malignant melanoma and meningioma; leukemia; other neoplasms	OS	*WRN*	AR

Abbreviations: ACC, adrenal cortical carcinoma; AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; OS, osteosarcoma.