CYTOGENETICS OF MESENCHYMAL TUMORS OF THE FEMALE GENITAL TRACT

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KEYWORDS

• Chromosomal aberrations • Translocation • FISH • Complex karyotype • Fusion gene

ABSTRACT

A great diversity of chromosome alterations have been reported in mesenchymal tumors of the female genital tract, particularly in the uterus. Some of these alterations specifically identify a certain tumor type. Cytogenetic studies on benign proliferations have not only demonstrated clonal chromosome changes, but have also pointed out clustering of aberrations to specific chromosome regions. For example, distinct cytogenetic subgroups have been described in uterine leiomyomas with overlapping histologic features. These findings may ultimately correlate with specific parameters, such as course of the disease, response to therapy, and recurrence. Moreover, such data may give a clue to an understanding of the biologic basis for distinctive behavior of benign versus malignant mesenchymal tumors. No specific chromosomal abnormalities have been described in malignant mesenchymal tumors, with the exception of low-grade endometrial stromal sarcomas. This article reviews the information currently available on genetic changes in mesenchymal tumors of the female genital tract and, more specifically, those reported in the uterus, where they have been more frequently studied.

OVERVIEW

A wide range of chromosome changes have been observed in mesenchymal tumors of the uterus (**Table 1**). The most extensive available cytogenetic data are for uterine leiomyomas. Unfortunately, cytogenetic data for other benign or malignant tumors of the female genital tract are scant because they are very rare.[1,2]

AGGRESSIVE ANGIOMYXOMA

A structural chromosome rearrangement of the 12q14∼15 region, with involvement of *HMGA2*, is the most frequent aberration observed in deep (aggressive) angiomyxoma of the vulvovaginal region.[3–7] Because the break on 12q14∼15 region could map inside or outside of HMGA2, fluorescence in situ hybridization analysis and immunohistochemical studies with an anti-HMGA2 antibody may not be diagnostically useful in all tumors.[4,7]

CELLULAR ANGIOFIBROMA

Partial loss of the long arm of chromosome 13 (eg, 13q−) has been reported by fluorescence in situ hybridization analysis in a single paravaginal cellular angiofibroma.[8] As this 13q− aberration has been also observed in spindle cell lipoma and in mammary and extramammary myofibroblastomas,[9–11] morphologic and cytogenetic similarities have been suggested among these three types of tumors.

UTERINE LEIOMYOMA INCLUDING VARIANTS

During the last two decades, uterine leiomyomas have been increasingly subjected to systematic cytogenetic analysis. To date, it has been possible to distinguish at least three cytogenetically

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Table 1
Specific chromosomal aberrations in mesenchymal uterine tumors

Tumor Type	Characteristic Cytogenetic Events	Molecular Events
Aggressive angiomyxoma	12q14∼15 involvement	*HMGA2* involvement
Leiomyoma	t(12;14)(q14∼15;q23∼24)/12q14∼15 rearrangement	*HMGA2* involvement
	del(7)(q22q32)	*CUTL1,ORC5L,DOCK4*
	6p21 rearrangement	*HMGA1* involvement
	Trisomy 12	Extra copies of *HMGA2*
	t(10;17)(q22;q23)	*MORF* involvement
	r(1)(p?q?)/1q-	Loss of *FH*
Atypical leiomyoma	1p- with -19 or -22	Unknown
Intravenous leiomyomatosis	der(14)t(12;14)(q14∼15;q23∼24)	Extra copies of *HMGA2*
Endometrial stromal tumor	t(7;17)(p15;q21)	*JAZF1-JJAZ1* fusion
	t(6;7)(p21;p15)	*JAZF1-PHF1* fusion
	t(10;17)(q22;p13)	Unknown

abnormal subgroups of uterine leiomyomas characterized by one of the following clonal abnormalities: (1) involvement of regions 12q14∼15, with t(12;14)(q14∼15;q23∼24) as the most often observed chromosomal translocation (**Fig. 1**); (2) interstitial deletion of the long arm (q) of chromosome 7 (**Fig. 2**), most frequently involving bands q22 and q32; and (3) rearrangement of 6p21, including translocations with 14q23∼q24 and other partners, as well as inversions (paracentric and pericentric) (**Fig. 3**). A variety of other cytogenetic abnormalities have been also reported, but with less frequency (eg, trisomy 12 [see **Fig. 1**]) rearrangements of 3q, 10q22, 13q, 1p, ring of chromosome 1, and Xp11∼p22).[2] The variety of chromosomal rearrangements suggests multiple genetic mechanisms for tumor initiation and growth in uterine smooth muscle cells and may explain clinical and pathologic differences in these tumors (eg, size, location, histology, or response to gonadotropin-releasing hormone (GnRH) agonists). Although no relationship has been identified between patient age or parity and type of chromosomal abnormality, it has been shown that: (1) uterine leiomyomas with chromosome 12 abnormalities are often larger than tumors with chromosome 7 abnormalities, and (2) larger leiomyomas are more likely to be chromosomally abnormal than smaller ones.[12–15]

Rearrangements involving 12q14∼15 and 6p21 are associated with aberrant expression of *HMGA2* and *HMGA1*, respectively. Both genes are members of the high mobility group (HMG) family of abundant, nonhistone components of chromatin, which acts as an architectural factor to influence diverse cellular processes. Rearrangement of both loci is a feature of most benign mesenchymal tumors.[16] HMGA2 and HMGA1 immunoreactivity correlates with cytogenetic abnormalities in several mesenchymal tumors of the female genital tract (eg, uterine leiomyoma, endometrial polyp, and aggressive angiomyxoma), as well as in other benign mesenchymal tumors carrying the same rearrangements (eg, lipoma, fibroadenoma, pulmonary chondroid hamartoma).[17] Genes associated with other rearrangements have yet to be defined. For example, a minimal common deleted region on 7q has been identified and narrowed down to 500 kilobases (kb).[18] Although several intriguing positional candidate genes have been identified (eg, *CUTL1, ORC5l, DOCK4*) in this gene-dense region, none has been proven to have a role in the genesis of leiomyomas carrying a 7q− aberration.[19]

A disruption of *MORF* at 10q22 has been reported in leiomyomas carrying a t(10;17)(q22;q23).[20] As linkage analyses have indicated, the fumarate hydratase (FH) gene, which is involved in Mendelian syndromes (eg, Reed syndrome [MIM150800] and hereditary leiomyomatosis and renal cell cancer [MIM605839]), is associated with uterine leiomyomas.[21,22] For this reason, attention has been focused on nonrandom occurrence of any rearrangement of the distal region of the long arm of chromosome 1 in q42-q44. Loss of *FH* at 1q42.1 has been observed in a subgroup of nonsyndromic uterine leiomyomas.[23]

Only a few cytogenetic studies have described changes associated with leiomyoma variants. Some tumors have shown chromosomal aberrations similar to those described in typical leiomyomas, such as rearrangement at 12q13-q15 in one bizarre leiomyoma,[24] in four lipoleiomyomas,[25–27] and one epithelioid leiomyoma.[28] Interstitial deletion of 7q has been reported in two epithelioid leiomyomas,[28] while markers and double minutes