Plasminogen Activator Inhibitor 1 Messenger RNA Expression and Molecular Evidence for del(7)(q22) in Uterine Leiomyomas

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ABSTRACT

We analyzed the expression of plasminogen activator inhibitor 1 (PAI-1) in 16 leiomyomas and adjacent myometrium of women who underwent a hysterectomy while in the proliferative (n = 8) and secretory (n = 8) phases of the menstrual cycle. We localized the PAI-1 and its mRNA expression in smooth muscle and vessel endothelial cells of uterine tissues using immunocytochemistry and in situ hybridization. The expression of PAI-1 mRNA was higher in 11 (68.75%) of 16 leiomyomas compared with the adjacent myometrium (leiomyoma/myometrium ratio, 1.4–3.0; mean, 2.045). The leiomyoma:myometrium ratio of PAI-1 mRNA expression did not change during the proliferative (Phase I) and secretory (Phase II) phases of the menstrual cycle. In the remaining five samples, the leiomyoma:myometrium ratio of PAI-1 mRNA expression was close to 1 (0.8–1.2; mean, 0.92). Because the locus of the PAI-1 gene is on chromosome 7q22, we screened for loss of heterozygosity (LOH) in these samples using the PAI-1 marker and D7S471, an anonymous marker 12 cm telomeric to PAI-1. Four of five samples with low leiomyoma:myometrium ratio had LOH for the PAI-1 and/or D7S471 markers. The fifth sample demonstrated a noninformative analysis for these markers but had LOH for the D7S15, D7S666, and D7S18 markers, all centromeric to PAI-1. Because del(7)(q22), associated with a relatively low PAI-1 mRNA expression, can deregulate matrix proteases and growth factors’ activity in leiomyomas, it is conceivable that del(7)(q22) results in heterogeneous leiomyoma biology.

INTRODUCTION

Leiomyomas are relatively avascular, tightly compacted tumors of smooth muscle cells that tend to be multiple and slow growing. Because all leiomyoma cells are of identical glucose-6-phosphate dehydrogenase electrophoretic type, the tumor has been considered to be of unicellular origin (1). The tendency of uterine leiomyomas to grow during the reproductive years and then regress after menopause suggests that sex steroid hormones are implicated in the pathophysiology of the disease (2). The putative increasing “intramyoma estrogen action” was attributed in part to inadequate metabolism of estradiol to estrone by the relatively small increase of 17β-hydroxysteroid dehydrogenase expression, an enzyme that metabolizes estradiol to estrone in leiomyomas compared with that of the myometrium during the secretory phase of the menstrual cycle (3). The assessment of the ER2 and progesterone receptor content in leiomyomas compared with that in the myometrium revealed conflicting data caused by either methodological pitfalls or the heterogeneous nature of the disease (4–8). The latter is possibly associated with variable regression of leiomyoma size in response to estrogen depletion therapies (9–13). Furthermore, the limited response of smooth muscle cells to estrogen treatment in vitro suggested that local growth factors probably mediate the remarkable response of the uterus, including leiomyoma regrowth after the cessation of estrogen depletion therapy in vivo (14–22). In this context, our previous studies documented that human leiomyoma extracts contained preferential growth factors for smooth muscle cells that were undetectable in myometrial and endometrial extracts (23–25). Recently, a novel leiomyoma-derived growth factor for human smooth muscle cells was directly implicated in the pathophysiology of uterine leiomyomas (26).

Although most uterine leiomyomas are of normal karyotype, there have been reports suggesting that 50% of the tumors bear specific chromosome aberrations (27–29). The leiomyoma cytogenetic profile has few similarities to malignant smooth muscle tumors but shares similarities to lipomas (27). Recently, a chromosomal analysis revealed the presence of clonal del(7)(q22) in approximately 34% of the leiomyomas (30). One of the genes mapped to 7q22 is the PAI-1 (31, 32) gene, a novel inhibitor of the conversion of plasminogen to plasmin by tPA and uPA (32). Plasmin, a broad-spectrum serine protease, in turn activates other matrix proteases such as collagenases (32) and growth factors such as the TGF-β family and IGF-1 and IGF II by limited hydrolysis of latent TGF-βs and IGFBP5s, respectively (32–36). There exist data implicating PAs and PAl in uterine development, growth, and involution (37–39).

In this study, we analyzed the expression of PAI-1 in leiomyomas and adjacent myometrium throughout the menstrual cycle. We found that the leiomyoma:myometrium ratio of PAI-1 mRNA expression is stable during the menstrual cycle and higher in the majority (68.75%) of leiomyomas as compared with the adjacent myometrium (leiomyoma:myometrium, 1.4–3). The leiomyoma:myometrium ratio of PAI-1 mRNA expression was relatively low in 5 of 16 leiomyomas (leiomyoma:myometrium, 0.8–1.2), a proportion similar to the frequency of del(7)(q22) in these tumors. Indeed, we detected molecular evidence of del(7)(q22) in this subgroup of leiomyomas. Because low versus high expression of PAI-1 leads to an altered homeostasis of protease and growth factor activity in the extracellular matrix, we postulate that variable PAI-1 expression possibly contributes in variant leiomyoma biology.

MATERIALS AND METHODS

Source and Handling of Tissues. Tissue samples of consecutive hysterectomies from women at the proliferative and secretory phases were analyzed in this study. Uterine tissues were obtained at the hysterectomy of premenopausal women harboring leiomyomas who had received no therapy prior to surgery. We obtained samples of eight leiomyomas and adjacent myometrium from women at the proliferative phase (Phase I) and eight leiomyomas and adjacent myometrium from women who underwent a hysterectomy while in the secretory phase (Phase II) of the menstrual cycle. The phase of the menstrual cycle was confirmed by the endometrial histology of the pathology material. The tissues were washed with HBSS and immediately processed or stored at −80°C without preservatives until use. This study was approved by
the local ethics committee (Laval University) according to the guidelines of the Medical Research Council of Canada for the use of human tissues in medical research. An informed consent was given by all subjects.

**In Situ Hybridization, Northern Blot Analysis, and Immunocytochemistry.** Because uterine tissues contain various fibrous components (especially leiomyomas) and PAI-1 was expressed also by the vessel endothelial cells of uterine tissues, we used *in situ* hybridization analysis to localize and evaluate PAI-1 mRNA expression in smooth muscle cells of leiomyoma and adjacent myometrium. The leiomyomal and myometrial tissues were embedded in OCT compound and mounted on a cryostat. Serial sections were cut (8-mm thick) at −16°C, collected on poly-L-lysine-coated slides, fixed for 20 min in 4% paraformaldehyde (w/v) in 0.1 m phosphate buffer at 4°C, and then washed in 0.1 m phosphate buffer for 20 min (4 times for 5 min each). Before hybridization the sections were washed first in 2× SSC solution (0.3 m sodium chloride and 0.03 m sodium citrate) and then in a 2× SSC solution containing 0.1% Triton X-100 for 10 and 20 min, respectively. Prehybridization was performed in a buffer solution containing 50% (v/v) formamide, 5× SSC, 0.18 m NaCl and 10 mm NaH2PO4, 1 mm EDTA, (pH 7.4), 0.1% SDS, 0.1% (w/v) polyvinylpyrrolidone, 200 µg/ml denatured salmon testis DNA, 2 mg/ml poly(AMP), 4% (w/v) dextran sulfate, and 10 mm DTT at RT for 2 h (26).

Two million counts of 35S-radiolabeled 217-bp cDNA probe (specific radioactivity: 1.3 x 10⁶ cpm/1.95 ng cDNA) corresponding to the 3' noncoding region of exon 9 of the human PAI-1 gene prepared by PstI digestion of the 5.2-kb cDNA EcoRI insert of human PAI-1 in the pUC9 vector (American Type Culture Collection, Bethesda, MD). This PAI-1 cDNA probe detects a 3.5-kb and 2.35-kb PAI-1 mRNA in human tissues, including the uterus, that simply represent different transcripts due to the presence of multiple polyadenylation splice sites (32). The radiolabeled PAI-1 cDNA probe was diluted in the prehybridization buffer and applied to each section. Hybridization was performed at 39°C for 16 h. After hybridization, the slides were washed at 20°C in (a) 2× SSC solution for 90 min at RT; (b) 1× SSC solution for 90 min at RT; and (c) 0.5× SSC solution for 60 min at RT, 0.5× for 60 min in 37°C; and 0.5× for 60 min at RT. The slides were rinsed with increasing concentrations of ethanol (70, 90, and 100%), air dried, and exposed to Kodak film for 14 days. The sections were coated with a Kodak NBT-2 liquid photographic emulsion diluted 1:1 with distilled water at 45°C and stored in darkness at 4°C. After 28 days of exposure, the slides were developed and stained with H&E. The slides used as negative controls (RNase) were pretreated with RNase A (10 µg/ml) and RNase T (100,000 units/ml) in 2× SSC for 45 min at 37°C. Leiomyomal, myometrial, and RNase slides (negative controls) were exposed to the same X-ray film. The intensity of the signals was analyzed using a PhosphorImager. The data were analyzed using ImageQuant Software v3.0 (Molecular Dynamics, Sunnyvale, CA). Signal intensity (absorbance/mm²) was evaluated by subtracting the respective RNase signal from each individual signal measurement in leiomyoma and myometrium tissues. The results were expressed as ratio of the leiomyoma:myometrium signal intensity in tissues from each hysterectomy based on the mean data of three different experiments on each tissue (mean leiomyoma:myometrium expression of human PAI-1 mRNA; Ref. 26).

**Immunocytochemistry.** was performed using cryostat sections of uterine tissues fixed in paraformaldehyde (4%) in 0.1 m phosphate buffer for 20 min. We analyzed PAI-1 expression using the commercially available goat polyclonal anti-human PAI-1 antibody, at a final dilution of 1:50 (American Diagnostics, Inc., Boston, MA), with the biotin-avidin-horseradish peroxidase method as described previously (26).

Molecular Evaluation of 7q22 Deletion. Deletion of the PAI-1 gene assessed by LOH at a highly polymorphic tetrancleotide repeat of the PAI-1 locus. In addition, we used D7S5471, an anonymous marker 12 cM telomeric to PAI-1, which consists of a dinucleotide repeat. We also used the anonymous D7S515, D7S666, and D7S518 markers centromeric to PAI-1 to analyze samples with a noninformative analysis for PAI-1 and D7S5471 markers and low leiomyoma:myometrium ratio of PAI-1 mRNA expression. DNA was purified from single 20-µm frozen histological sections of leiomyomas and the adjacent myometrium after digestion with protease K. The polymorphic repeat sequences were amplified using PCR primers from Research Genetics (Huntsville, AL) on the sequence provided by the Genome Data Base at Johns Hopkins University (D7S5471, AGACGCTATTTGGAAATTGC/CAA- CATATGCAAGGTGCTCTA: D7S515, GGGAGGCTACTACCCCTAACTTTA- ATGGGACTGCTCGGGAACAG: D7S518, CAGTAGGCGAGGTTGGG- GGTGTTGTCCTGTTGTGAAC: D7S666, CAGGCTCAAAGAAATTCGATCC- TGATAGCTGATTGAGGAAAGAG: and PAI-1, GATAGGAGCAGACGAGGAG- GAACAGAATGTT). The amplification products were internally labeled by the inclusion of [32P]dATP in the PCR mix and separated on a sequencing gel (31, 40).

**RESULTS**

The expression of PAI-1 was detected using immunocytochemistry in leiomyoma and adjacent myometrium. The expression of PAI-1 was evident in the smooth muscle cells of myometrium and leiomyoma as well as in the endothelial cells of blood vessels nourishing the leiomyomas and adjacent myometrial tissues. Vessel smooth muscle cells did not express PAI-1 as analyzed using immunocytochemistry (Fig. 1).

Because leiomyomal and myometrical tissues contained (a) vessel endothelial cells expressing PAI-1 and (b) various fibrous component (mainly the leiomyomas), we used *in situ* hybridization analysis to compare the PAI-1 mRNA expression in the uterine smooth muscle cells. Therefore, we used *in situ* hybridization analysis to localize and specifically analyze leiomyoma:myometrium ratios of PAI-1 mRNA expression in the uterine smooth muscle cells (Fig. 2).

Indeed, we localized the PAI-1 mRNA expression in smooth muscle cells of both the leiomyomal and adjacent myometrical tissues (Fig. 2). We found that the relative expression of PAI-1 mRNA was higher in the majority of leiomyomas as compared with that of the adjacent myometrium (11/16, 68.75%), ranging the leiomyoma:myometrium ratios from 1.4 to 3; the mean leiomyoma:myometrium ratio was 2.045 (Fig. 3). The leiomyoma:myometrium ratio was higher in 5 (62.5%) of 8 samples obtained from women while in Phase I and 6 (75%) of 8 samples from women who had undergone a hysterectomy while in Phase II of the menstrual cycle. Analysis of the relative expression of PAI-1 mRNA in these tissues revealed that the mean leiomyoma:myometrium ratio was stable throughout the menstrual cycle (leiomyoma/myometrium, 2.02 and leiomyoma/myometrium, 2.06).

In contrast, the PAI-1 mRNA expression was relatively low (leiomyoma:myometrium ratios ranging from 0.8 to 1.2; mean, 0.92) in 5 (31.25%) of 16 leiomyomas. This was evident in three of eight samples from women in Phase I (mean leiomyoma:myometrium ratio, 0.93) and two of eight samples from women who underwent a hysterectomy while in Phase II of the menstrual cycle (leiomyoma/myometrium, 0.9; Ref. 3).

Because 7q22 is the locus of PAI-1, we analyzed the possible loss of LOH using D7S5471 and D7S471, a marker 12 cM telomeric to PAI-1. Both markers have six alleles, all common. Nine samples were informative for PAI-1 and D7S471 (Table 1). Of these, three (samples 10, 13, and 14) had LOH for PAI-1 and one (sample 11) for D7S471 that was noninformative for PAI-1 (Fig. 4). Sample 10 had LOH for both the PAI-1 and D7S471 markers (Fig. 4). All four of these samples belonged to the subgroup uterine tissues with leiomyoma:myometrium ratios of PAI-1 mRNA expression close to 1 (Table 1). The fifth sample (sample 9) also presented with a leiomyoma:myometrium ratio close to 1 but had a noninformative analysis for both the PAI-1 and D7S471 markers. Genotyping analysis enabled us to detect LOH in sample 9 for the D7S3515, D7S666, and D7S518 markers, all centromeric to PAI-1 (Table 1).

The 11 leiomyomas that belonged to the high-expressing group of PAI-1 mRNA (leiomyoma:myometrium ratios ranging from 1.4 to 3)
Fig. 1. Examples of the PAI-1 expression as detected by immunocytochemistry using a goat anti-human PAI-1 antibody (details in "Materials and Methods"). A, expression of PAI-1 in myometrium was documented in the vessel endothelial cells (vec) and smooth muscle cells of human myometrium (smc). Note that the vessel smooth muscle cells (vsmc) did not express PAI-1 as assessed using immunocytochemistry. In some cases, the expression of PAI-1 was apparently higher in leiomyoma (A) as compared with that of the adjacent myometrium (B), and in other cases PAI-1 expression did not differ between the leiomyomas (C) and adjacent myometrial tissues (D). F, example of negative control analysis; omission of the anti-PAI-1 antibody. E, ×80; A, B, C, D and F × 400.

were either confirmed disomic at PAI-1 (6 samples: 1, 3, 5, 8, 15, and 16), D7S471 (7 samples: 1–6 and 16) or had a noninformative analysis for either markers (2 samples: 7 and 12) (Table 1). The higher (30%) than expected (15%) incidence of noninformative analysis (homozygosity) in these tumors for the PAI-1 and D7S471 markers was possibly suggestive of the distinct genetic background of French-
Fig. 2. An example of the analysis for PAI-1 mRNA expression in the smooth muscle cells of leiomyoma and adjacent myometrium as assessed using in situ hybridization. Light microscopic micrographs of PAI-1 mRNA expression in leiomyoma (A1) and adjacent myometrium (A2). A3, negative control analysis; slide pretreated with RNase (see details in "Materials and Methods"). The autoradiographs B1–3 show the detection of the radioactive signal representing PAI-1 mRNA expression as detected on the film. B1, leiomyoma; B2, adjacent myometrium; and B3, RNased negative control. A1–3, ×800.

L/M RATIO OF PAI-1 mRNA EXPRESSION

Fig. 3. Analysis of PAI-1 mRNA expression (leiomyoma: myometrium ratios) as assessed using in situ hybridization (Fig. 2). The majority (11/16 samples: 1–8, 12, 15, and 16) of uterine tissues had leiomyoma:myometrium ratios of PAI-1 mRNA expression greater than 1 (range, 1.4–3.0). Of these, samples 3, 5, 8, 12, and 16 were from women in Phase I, and samples 1, 2, 4, 6, 7, and 15 were from women who underwent a hysterectomy while in Phase II of the menstrual cycle. Note that five samples presented with leiomyoma:myometrium ratios of PAI-1 mRNA expression close to 1 (samples 9, 10, 11, 13, and 14). Of these, samples 10, 13, and 14 were from women in Phase I, and samples 9 and 11 were from women who underwent a hysterectomy while in Phase II of the menstrual cycle. These data indicated that there existed a subgroup of leiomyomas with a relatively low PAI-1 mRNA expression.

Table 1. LOH for 7p22 as analyzed by PAI-1 and D7S471 markers and expression of PAI-1 mRNA in uterine leiomyomas

<table>
<thead>
<tr>
<th>Sample</th>
<th>Leiomyoma:myometrium</th>
<th>LOH for PAI-1</th>
<th>LOH for D7S471</th>
</tr>
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<tr>
<td>1</td>
<td>2.5</td>
<td>Disomic</td>
<td>Disomic</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>Noninformative</td>
<td>Disomic</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>Disomic</td>
<td>Disomic</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>Noninformative</td>
<td>Disomic</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>Disomic</td>
<td>Disomic</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>Noninformative</td>
<td>Disomic</td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>Noninformative</td>
<td>Noninformative</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>Disomic</td>
<td>Noninformative</td>
</tr>
<tr>
<td>9</td>
<td>0.9</td>
<td>Noninformative</td>
<td>Noninformative</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
<td>Deleted</td>
<td>Deleted</td>
</tr>
<tr>
<td>11</td>
<td>0.9</td>
<td>Noninformative</td>
<td>Deleted</td>
</tr>
<tr>
<td>12</td>
<td>2.3</td>
<td>Noninformative</td>
<td>Noninformative</td>
</tr>
<tr>
<td>13</td>
<td>1.2</td>
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<tr>
<td>14</td>
<td>0.8</td>
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</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>Disomic</td>
<td>Noninformative</td>
</tr>
<tr>
<td>16</td>
<td>2.0</td>
<td>Disomic</td>
<td>Disomic</td>
</tr>
</tbody>
</table>

* Sample 9 had LOH for D7S515, D7S666, and D7S518 markers centromeric to PAI-1.

Canadian living in the major Quebec City area (95% of the overall population) reflected in our tissue samples.

The group of leiomyomas with low PAI-1 leiomyoma:myometrium ratios and del(7)(q22) presented with histopathological features similar to those of the majority of leiomyomas (with high leiomyoma:myometrium ratios; Table 2).

DISCUSSION

The pathogenesis of uterine leiomyomas remains unknown. Histologically, leiomyomas are tightly compacted tumors composed of smooth muscle cells presenting various degrees of cellularity (1, 2). Data exist to indicate the role of sex steroid hormones in the development, evolution, and involution of the disease (2–8). Interestingly, the leiomyoma response to estrogen deprivation therapy suggested that not all tumors show a similar degree of regression, suggestive of heterogeneous tumor biology. It is important to note that the leiomyoma response to estrogen depletion therapy is not associated with a particular type of leiomyoma histology (14–22).

Recently, cytogenetic evidence showed the heterogeneous nature of leiomyomas by detecting several types of distinct chromosomal abnormalities in leiomyomas (27–30). Of them 34% involved
del(7)(q22) (30). These data were suggestive of ablation of the expression of genes localized in this particular locus, such as PAI-1, multiple drug resistance 1 and 2, erythropoietin, collagen type 1α2, heparin-binding neurite outgrowth-promoting factor, and CCAAT displacement protein gene (CUTL1), a putative suppressor gene with tissue-specific expression (30, 31). Because most of the uterine leiomyomas have an apparently normal karyotype, the molecular consequences of these chromosomal abnormalities should contribute to heterogeneous tumor biology rather than the pathogenesis of the disease (15, 30).

One of the genes in the 7q22 locus is the PAI-1, an important inhibitor of plasminogen transformation to plasmin by tPA and uPA (31, 32). Plasmin is a powerful broad-spectrum protease that triggers an important biological response of the extracellular matrix not only by mediating the activation of various matrix proteases, thus resulting in fibrinolysis, tissue involution, and cancer invasion, but also by activating growth factors such as the family of TGF-βs and IGFs resulting in tissue remodeling, regeneration, and metastatic growth (32–39). Both the PAs (tPA and uPA) are sex steroid hormone-regulated genes in the human uterus (37–39).

In this context, our results which detected approximately 35% of the leiomyomas expressed relatively low levels of PAI-1 mRNA in leiomyomas, described previously (30) to have del(7)(q22) (locus of PAI-1), we further analyzed loss of LOH using the PAI-1 marker and D7S471, a marker telomeric to PAI-1. Indeed, we detected LOH for the PAI-1 and D7S4721 markers in four of five leiomyomas in this group. The fifth had a noninformative analysis by these markers but included 7q22, the cytogenetic location of PAI-1. Therefore, the molecular evidence that subgroups of leiomyomas contain low or high expression of PAI-1 mRNA is suggestive of a variant leiomyoma response to matrix protease(s) and growth factor activity.

The analysis of pathological data in the leiomyomas expressing low and high PAI-1 mRNA expression more or less stable during the menstrual cycle, suggesting that sex steroid hormones either do not control PAI-1 mRNA expression or exert similar modulation in PAI-1 mRNA expression in both leiomyomas and adjacent myometrium. Therefore, the majority of leiomyomas do not apparently differ from the adjacent myometrium with respect to PAI-1 mRNA expression throughout the menstrual cycle. These data suggested that if there exists a deregulation of the plasminogen/plasmin system in leiomyomas throughout the menstrual cycle as reported previously (37–39), this is possibly produced by changes of the tPA and uPA mRNA expression in leiomyomas.

In addition, the higher PAI-1 expression documented in the majority of the leiomyomas as compared with that of the adjacent myometrium throughout the menstrual cycle is possibly part of a leiomyoma-specific feedback mechanism triggered by increasing protease(s) and growth factor(s) activity locally. Obviously, this local feedback mechanism would be impaired in leiomyomas bearing del(7)(q22). Therefore, the molecular evidence that subgroups of leiomyomas contain low or high expression of PAI-1 mRNA is suggestive of a variant leiomyoma response to matrix protease(s) and growth factor activity.

The leiomyoma:myometrium ratio of the PAI-1 mRNA expression was more or less stable during the menstrual cycle, suggesting that sex steroid hormones either do not control PAI-1 mRNA expression or exert similar modulation in PAI-1 mRNA expression in both leiomyomas and adjacent myometrium. Therefore, the majority of leiomyomas do not apparently differ from the adjacent myometrium with respect to PAI-1 mRNA expression throughout the menstrual cycle. These data suggested that if there exists a deregulation of the plasminogen/plasmin system in leiomyomas throughout the menstrual cycle as reported previously (37–39), this is possibly produced by changes of the tPA and uPA mRNA expression in leiomyomas.

The analysis of pathological data in the leiomyomas expressing low and high PAI-1 mRNA expression reveal no significant differences (Table 2). Therefore, it is conceivable that putative variant leiomyoma biology in these leiomyomas is possibly linked with other aspects of tumor biology. Because evidence now exists to suggest that growth factors and matrix proteases mediate sex steroid hormone response in various tissues, including the uterus (14–26, 33–39), it is conceivable that the subgroup of leiomyomas with del(7)(q22) possibly contributes to an heterogeneous leiomyoma response to estrogen depletion therapy.

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