THEMATIC REVIEW

RISING STARS

Role of MED12 mutation in the pathogenesis of uterine fibroids

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This paper is part of a collection of articles highlighting the breadth and depth of research being undertaken across the field of basic endocrinology by early- and mid-career researchers. The collection is published across the Journal of Endocrinology and the Journal of Molecular Endocrinology.

Graphical abstract

MED12 mutation positive uterine fibroids (MED12-UFs)

Characteristics of MED12-UFs
- More common in Black women
- Multiple rather than solitary
- Higher shrinkage rate by ulipristal acetate

Effects of introduction of MED12 mutation in myometrial cells
- Wnt/β-catenin signaling ↑
- mTOR signaling ↑
- Cell-cycle ↑
- Type 1 collagen production ↑

Expression of ECM-related genes ↑
Deposition of ECM ↑
CDK activity ↓
Dysregulation of Wnt/β-catenin signaling
Changes in DNA methylome, transcriptome, and proteome
Abstract

Uterine fibroids (UFs) are benign tumors arising from the uterus, characterized by accumulation of abundant extracellular matrix (ECM) and sex steroid-dependent growth. Women with symptomatic UFs have reduced quality of life and decreased labor productivity. Among the driver gene mutations identified in UFs, mutations in MED12, a component of the cyclin-dependent kinase (CDK) Mediator module, are the most common and observed in 50–80% of UFs. They are gain-of-function mutations and are more frequently observed in Black women and commonly observed even in small UFs. MED12 mutation-positive UFs (MED12-UFs) often develop multiple rather than solitary and have distinct gene expression profiles, DNA methylomes, transcriptomes, and proteomes. Gene expressions related to ECM organization and collagen-rich ECM components are upregulated, and impaired Mediator kinase activity and dysregulation of Wnt/β-catenin signaling are identified in MED12-UFs. Clinically, the UF shrinking effect of gonadotropin-releasing hormone agonists and ulipristal acetate is dependent on the MED12 mutation status. Understanding of characteristics of MED12-UFs and functions of MED12 mutations for UF tumorigenesis may elucidate the pathophysiology of UFs, leading to the development of new therapeutic options in women with symptomatic UFs.

Key Words
- female reproduction
- Mediator complex
- progesterone
- uterine fibroid
- Wnt signaling pathway

Invited author's profile

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Kaori Koga MD PhD is Chair and Professor of the Department of Reproductive Medicine (Obstetrics and Gynecology), Graduate School of Medicine, Chiba University, Chiba, Japan. Dr Koga received her MD from Chiba University in 1996 and her PhD from the University of Tokyo in 2003. She then undertook post-doctoral fellowships in the Uterine Biology Group (Professor Lois Salamonsen's laboratory) at Prince Henry’s Institute, Melbourne, Australia in 2006, and the Reproductive Immunology Unit (Professor Gil Mor's laboratory) at Yale University, USA, 2006–2008. Her research interests include the pathogenesis of endometriosis, fibroids and infertility, and the assessment of their medical and surgical management. Dr Koga is the author or co-author of more than 200 scientific articles published in peer-reviewed international journals, such as Proceedings of the National Academy of Sciences and Nature Reviews Disease Primers. Dr Koga is a board member of the World Endometriosis Society and the Society of Endometriosis and Uterine Disease, a member of the American Society of Reproductive Immunology and the International Society for Immunology of Reproduction.
**Introduction**

Uterine fibroids (UFs), also called uterine leiomyomas, are the most common gynecological tumors in women, characterized by the deposition of abundant extracellular matrix (ECM) and intratissue hypoxia (Mayer et al. 2008). Up to 75% of women worldwide have UFs, and many women with symptomatic UFs suffer from heavy menstrual bleeding, iron deficiency anemia, and subfertility (Stewart & Nowak 2022). These symptoms not only reduce the quality of life in women of reproductive age but also decrease women's labor productivity which leads to significant economic losses (Tanaka et al. 2013). UFs rarely develop before menarche, frequently increase in size during reproductive age, and mostly shrink after menopause, indicating that sex steroids, namely, estrogen and progesterone, play crucial roles in the growth and enlargement of UFs. Epidemiological studies have revealed that Black ethnicity, advanced age, obesity, nulliparity, family history of UFs, hypertension, and frequent soybean milk intake are risk factors for UFs. Frequently occurring menstruation caused by early menarche and declining birthrates in modern women may also increase the prevalence of UFs. On the other hand, common use of oral contraceptives, smoking, sexual prolificacy, and lean body mass are thought to be protective factors against UFs (Yang et al. 2022).

Driver gene mutations occur early in tumorigenesis and significantly affect tumors’ development and subsequent progress. Four distinct driver gene mutations have been identified in UFs: mutations in MED12, overexpression of high mobility group AT-hook 2 (HMGA2) caused by chromosomal rearrangement, biallelic loss of fumarate hydratase (FH), and deletions of collagen type 4 alpha 5 chain (COL4A5)-collagen type 4 alpha 6 chain (COL4A6) (Mehine et al. 2016) (Table 1). Somatic mutations in MED12, the Mediator complex subunit 12 gene, are frequently observed in 50–80% of UFs. MED12 is located on chromosome Xq13.1 and is one of the subunits of the Mediator, an RNA polymerase II activator-interacting multiprotein complex involved in transcriptional regulation and gene expression. Many studies have been conducted to investigate the characteristic differences between MED12 mutation-positive UFs (MED12-UFs) and the mutation-negative (wild-type) UFs (wt-UFs) and the functional roles of these mutations for the tumorigenesis of UFs. Here, we review the recent advances in the research of the pathophysiology of UFs associated with the MED12 mutations.

**Driver gene mutations in UFs**

MED12 mutations are considered as the most frequent driver gene mutation. Although the precise mechanisms of why they frequently occur in UFs remain unknown, a recent study revealed that oxidative stress induced gene mutations in myometrial cells in vitro. Moreover, a significantly higher expression of reactive oxidative species was identified in the adjacent myometrium of UFs compared with that without UFs, indicating that myometrial oxidative stress may promote MED12 mutations in the myometrium with UFs (Li et al. 2022). This may be one of the possible mechanisms that drive MED12 mutations in UFs.

The frequency of other mutations is estimated to be considerably low: overexpression of HMGA2, mostly caused by chromosomal rearrangement of 12q15, is estimated as 10–20%, biallelic inactivation of FH, which leads to complete loss of fumarate hydratase activity is 1–2%, and deletions of COL4A5-COL4A6 that are observed in women with Alport syndrome developing multiple fibroids in the uterus and esophagus, is less than 1%. Each gene alteration has been reported to

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene</th>
<th>Type of mutation</th>
<th>Frequency</th>
<th>Function of mutation</th>
<th>Related syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED12</td>
<td>Mediator complex 12</td>
<td>Missense mutation</td>
<td>50–80%</td>
<td>Gain of function</td>
<td>Hereditary leiomyomatosis and renal cell cancer</td>
</tr>
<tr>
<td>HMGA2</td>
<td>High mobility group AT-Hook 2</td>
<td>Chromosomal rearrangement</td>
<td>10–20%</td>
<td>Overexpression</td>
<td></td>
</tr>
<tr>
<td>FH</td>
<td>Fumarate hydratase</td>
<td>Chromosomal translocation Biallelic loss</td>
<td>1–2%</td>
<td>Loss of fumarate enzymatic activity</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>COL4A5/COL4A6</td>
<td>Collagen type 4 alpha 5 chain/collagen type 4 alpha 6 chain</td>
<td>Deletions</td>
<td>Less than 1%</td>
<td>Unknown</td>
<td></td>
</tr>
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Table 1 Driver gene mutations observed in uterine fibroids.
be mutually exclusive to each UF nodule in the earlier studies (Kämpjärvi et al. 2016, Bertsch et al. 2014, Mäkinen et al. 2017); however, subsequent studies have reported that overexpression of HMGA2 is observed in MED12-UFs (Galindo et al. 2018). This finding appears to contradict the notion that driver gene mutations are mutually exclusive. The overexpression of HMGA2 is not only induced by chromosomal rearrangement affecting 12q15 that leads to translocation of HMGA2 but also caused by dysregulation of micro RNAs (miRNAs). The overexpression of HMGA2 in MED12-UFs is induced by the dysregulation of miRNAs that negatively regulate HMGA2 gene transcription (Mello et al. 2018). Neither biallelic loss of FH nor deletions of COL4A5-COL4A6 have been observed in MED12-UFs.

**Characteristics of MED12-UFs**

The MED12-UFs have distinct characteristics compared with wt-UFs and adjacent myometrial tissues. They occur in a multiple rather than solitary manner. Mutations in MED12 are frequently observed even in small-sized UFs with a diameter of <3.0 cm, consistent with driver gene mutations. The ratio of MED12-UFs to wt-UFs was significantly higher in subserosal UFs than in intramural UFs (Heinonen et al. 2017). Further, MED12-UFs are more frequently observed in Black women compared with White and Asian women, but no significant relationship was identified between the frequency of mutations and women's age and body mass index (He et al. 2022). Integrative analyses have revealed altered gene expression profiles and DNA methylation status based on the MED12 mutation status in UFs. MED12-UFs have distinct DNA methylome and transcriptome compared to those of wt-UFs and adjacent myometrium (Carbajo-García et al. 2022, Maekawa et al. 2022). High-throughput sequencing of RNA transcripts revealed differential gene expression between MED12-UFs and wt-UFs, and between myometrium adjacent to MED12-UFs and that adjacent to wt-UFs. Genes related to the regulation of ECM constituents were uniquely expressed in the MED12-UFs, and the genes involved in the response to oxygen-containing compounds and the extracellular space were differentially expressed between the two different adjacent myometrium (Chuang et al. 2023). Moreover, MED12-UFs have increased ECM organization, cell adhesion, integrin-mediated signaling pathway, Wnt/β-catenin signaling pathway, and response to estrogen, whereas wt-UFs have increased angiogenic activities and smooth muscle cell proliferation. Collagen fibers were more enriched in the MED12-UFs than those in the wt-UFs and in the myometrium. On the contrary, the number of blood vessels was significantly lower in the MED12-UFs than those in the wt-UFs (Maekawa et al. 2022). Another study revealed that higher vessel maturity was observed in the MED12-UFs compared with wt-UFs, though vessel density did not significantly change (Nagai et al. 2022).

Clinically, the MED12 mutation status influences the effects of hormone therapy for UFs. MED12-UFs became smaller in response to ulipristal acetate, a selective progesterone receptor (PR) modulator that shrinks UFs, as compared to HMGA2 overexpressing UFs. ChIP-seq revealed that PR-binding sites were less methylated in MED12-UFs than in normal myometrium or in HMGA2 overexpressing UFs. A principal component analysis of 48 progesterone pathway-related genes and 84 genes involved in ECM remodeling between MED12-UFs and HMGA2 overexpressing UFs showed distinct expression properties in both types of UFs (Kolterud et al. 2023). Another study revealed that MED12-UFs with a diameter of ≥5 cm showed smaller volume reductions after treatment with gonadotropin-releasing hormone (GnRH) agonists than those of wt-UFs. Most of the MED12-UFs demonstrated low signal intensity, while most of the wt-UFs demonstrated high signal intensity on non-contrast-enhanced T2-weighted magnetic resonance imaging (MRI) before GnRH agonist treatment. The volume reduction rate of T2-weighted MRI low-intensity UFs was significantly lower than those of high-intensity UFs. The MED12 mutation status, together with the MRI findings, is a possible biomarker for the responsiveness to GnRH agonists (Nagai et al. 2022).

**Functional roles of MED12 mutations in UFs**

Whole exome sequencing revealed that hot spots of the mutations in MED12 are located on exon 2, and missense mutations in codons 35, 43, and 44 are frequently observed in UFs (Mäkinen et al. 2013). These mutations do not affect protein expression levels of MED12 (Croce and Chibon, 2015), indicating that they have functional roles in the tumorigenesis of UFs without alteration of the protein expression. MED12 is a component of the kinase module of the Mediator, which consists of cyclin-dependent kinase 8 (CDK8), cyclin C, and the MED12 and MED13 subunits (Malik and Roeder, 2010). MED12 activates the kinase activity of the CDK8 in the
Mediator via direct interaction with cyclin C, and the Mediator kinase activity is selectively disrupted in MED12-UFs (Park et al. 2018a). Mutations in MED12 disrupt the MED12–cyclin C interface, leading to the alteration of CDK8 T-loop stabilization and inactivation of CDK8 kinase activity in the cultured cells (Turunen et al. 2014). In addition, MED12-UFs exhibited significantly higher levels of R-loops and impaired replication fork dynamics compared to wt-UFs. Mediator kinase inhibition triggered aberrant R-loop-induced replication stress, leading to genomic instability (Muralimanoharan et al. 2022). Alternatively, they promoted dissociation of the activation loop, leading to inactivation of CDK8 kinase activity (Gonzalez et al. 2022). Furthermore, they disrupted the binding of cyclin C–CDK19, a paralog of CDK8 that was expressed in both myometrium and UFs and disrupted the CDK19 kinase activity (Park et al. 2018b). These results indicate that the cyclin-C–CDK8/CDK19 activity is disrupted by multiple processes in MED12-UFs, and the impairment of kinase activity negatively affects the function of Mediator.

The introduction of MED12 mutations in cultured myometrial cells and mouse models revealed distinct roles of these mutations for the UF-related properties (Fig. 1). In vitro experiments using immortalized human myometrial smooth muscle cells overexpressing either wild-type MED12 or MED12 variant (c.131G>A), which is the most common mutation observed in UFs, revealed that protein expression levels of Wnt4 and β-catenin increased and the cell cycle progressed in the MED12 variant-overexpressing cells. Protein levels of mammalian target of rapamycin (mTOR) signaling pathways also increased in the MED12 variant-overexpressing cells, indicating that the MED12 mutations have a potential for myometrial cell transformation to UFs by dysregulating the Wnt/β-catenin and mTOR signaling pathway (El Andaloussi et al. 2020). Moreover, gain-of-function mutations in MED12 using CRISPR/Cas9 system enhanced type 1 collagen production, whereas cell proliferation speed did not change in patient-derived myometrial cells. Collagen production became more active in the presence of estrogen and progesterone, and TGFβ3, of which the expression is upregulated in UFs, in the cultured media (Takao et al. 2022). A mouse model that conditionally expresses a Med12 missense variant (c.131G>A) in the uterus on a background of Med12 knockout demonstrated that UFs form in the uterus as early as 8 weeks of age,

![Image](https://jme.bioscientifica.com)

**Figure 1**

Effects of introduction of MED12 mutations in cultured myometrial cells and mouse model. MED12 mutations identified in UFs are thought to be gain-of-function mutations. The introduction of MED12 mutations in myometrial cells increases the Wnt/β-catenin signaling pathway and protein levels of mammalian target of rapamycin (mTOR) signaling pathways, enhances type 1 collagen production, leads to genomic instability, cell cycle progression, and inhibition of autophagy, whereas cell proliferation speed is not affected.
and 80% of uteri have multiple UF-like structures consisting of ECM deposits, infiltration of fibroblasts and macrophages, and disorganized muscle fiber arrangement, accompanied by the destruction of myometrial architecture. The same Med12 variant also caused UFs in mice on a background of wild type Med12, but compared to those on a background of Med12 knockout, the timing of UF-like structure formation in the uterus was later and the size of the UF-like region was smaller. These results indicate that the Med12 missense c.131G>A variant acts as a gain-of-function mutation in the uterus of mice (Mittal et al. 2015).

Dysregulation of Wnt/β-catenin signaling in MED12-UFs

The Wnt/β-catenin signaling pathway is evolutionarily conserved in mammals and regulates diverse developmental processes, including proliferation, differentiation, apoptosis, migration, invasion, and tissue metabolism and homeostasis. It also plays a crucial role in tumorigenesis, and dysregulation of this cascade may initiate the progression of malignant tumors. Differential gene expression of Wnt signaling components and overexpression of β-catenin both at the RNA and protein levels was observed in UFs compared to adjacent myometrium (Ko et al. 2018). Overexpression of Wnt4, Wnt5a, and Wnt5b has been observed in cultured UF cells compared with that in the adjacent myometrial cells (Ono et al. 2013). Furthermore, sex steroids regulate Wnt/β-catenin signaling in UFs. Administration of 17β-estradiol induces in cultured UF cells, which can be reversed by an estrogen receptor antagonist. The simultaneous addition of estrogen and progesterone induces nuclear translocation of β-catenin and stimulates the Wnt/β-catenin signaling cascade in UF cells (Ali et al. 2020).

The Mediator complex regulates Wnt/β-catenin signaling in many tissues, and MED12 directly binds to the β-catenin transactivation domain, indicating that mutations in MED12 affect the Wnt/β-catenin signaling pathway in UFs. Overexpression of β-catenin in UFs was independent of the MED12 mutation status, and the expression of the Wnt pathway components was downregulated in MED12-UFs compared to those in wt-UFs (Ko et al. 2018). Another study revealed that protein expression of Wnt4 was higher in MED12-UFs compared with those with overexpression of HMGA2 (Markowski et al. 2012). Furthermore, Wnt4 and β-catenin were significantly upregulated in MED12-UFs compared to adjacent myometrium (Corachán et al. 2021). Induction of the MED12 mutations activates Wnt/β-catenin signaling in immortalized human myometrial smooth muscle cells through increased levels of protein expression of Wnt4 and β-catenin (El Andaloussi et al. 2020). Silencing MED12 expression using MED12 shRNA reduces the protein expression of Wnt and β-catenin and cell proliferation in cultured UF cells (Al-Hendy et al. 2017). Because the Wnt/β-catenin signaling pathway exhibits cross talk with other signaling pathways, including the TGF-β, PI3K/Akt/mTOR, MAPK, IGF, Hippo, and Notch signaling pathways, the dysregulation of Wnt/β-catenin signaling pathway plays important roles for the growth and maintenance of MED12-UFs.

Progesterone-dependent growth in MED12-UFs

Sex steroid-dependent growth is another characteristic of UFs. Both estrogen and progesterone maintain the growth of UFs. Estrogen promotes the growth of UFs and induces the expression of PRs. Progesterone/PR signaling also maintains the growth of UFs (Ishikawa et al. 2010). A study using a patient-derived xenograft (PDX) model in immunodeficient mice revealed that 17β-estradiol and progesterone maintain the growth of MED12-UFs mediated by the IGF pathway. Interestingly, the survival of UF cells in the PDX derived from MED12-UFs was independent of 17β-estradiol and progesterone, and shrinkage of the PDX after removing 17β-estradiol and progesterone was mainly due to size reduction of UF smooth muscle cells and decrease of ECM components, indicating that the sex steroid-dependent growth of MED12-UFs was regulated by the increase and regression of smooth muscle cells and ECM independent of the cell survival (Serna et al. 2018).

MED12 mutation status may affect the progesterone/PR signaling in UFs. MED12-UFs have higher treatment response rates for ulipristal than those in HMGA2-overexpressing and wt-UFs. MED12-UFs have distinct characteristics regarding progesterone-dependent growth and ECM formation compared to the HMGA2-overexpressing UFs (Kolterud et al. 2023). The receptor activator of nuclear factor κB ligand (RANKL) is a progesterone/PR signaling target gene, and its expression is differentially regulated by progesterone/PR signaling between UFs and the myometrium. The highest receptor activator of nuclear factor κB (RANK) levels were found in the UF stem cell population, and the highest RANKL levels were found in the PR-rich UF.
cell population. Blocking the RANKL/RANK pathway inhibited the progesterone-dependent growth of UFs in the PDX model (Ikhena et al. 2018). MED12 mutation status influences RANKL transcription and its interaction with PR. RANKL mRNA expression levels were significantly higher in tissues carrying MED12-UFs than those carrying wt-UFs. PR interacted with MED12, and the interaction was stronger in MED12-UFs. These indicate that the more prominent anti-tumor effect for the inhibition of the RNAKL/RANK pathway can be observed in MED12-UFs (Liu et al. 2019). The tryptophan catabolism pathway, which is essential for protein synthesis and serotonin production, is dysregulated in MED12-UFs. Expression levels of tryptophan 2,3-dioxygenase-2 (TDO2), a tryptophan degradation enzyme that catalyzes the oxidation of L-tryptophan to N-formyl-L-kynurenine, are upregulated in cultured UF cells originated from MED12-UFs. Progestins inhibit TDO2 gene expression in myometrial cells and wt-UF cells but not in MED12-UF cells. MED12 mutations may impair progesterone signaling in UFs that regulate TDO2 gene expression, leading to upregulated TDO2 gene expression following decreased tryptophan levels in MED12-UFs. These studies indicate that progesterone/PR signaling is varied from MED12 mutation status in UFs, and it may alter progesterone-mediated TDO2 expression in UFs (Hutchinson et al. 2022).

**Role of MED12 mutations in extracellular matrix formation**

Enrichment of ECM is another characteristic of UFs, and collagen, proteoglycan, fibronectin, laminin, and others are composed of ECM in UFs. Deposition of excessive amounts of ECM maintains not only the volume and density of UFs but also the microenvironment and response of UF smooth muscle cells that is mediated by growth factors, cytokines, and hormones. These mediators also play important roles in the formation of ECM in UFs. Higher expression of TGF-β1 and β3, activin A, platelet-derived growth factor, and tumor necrosis factor alpha in UFs compared with those in the myometrium has been identified, and this affected the production of collagen, fibronectin, and other ECM components in UFs (Islam et al. 2018).

The impact of mutations in MED12 on the composition of the ECM is still debatable. Comparative genomic and transcriptomic analyses between MED12-UFs and wt-UFs revealed that genes related to the ECM organization, collagen catabolic process, and canonical Wnt signaling pathway were upregulated in the MED12-UFs (Maekawa et al. 2022). Another comparative proteomics analysis between UF tissues (small, medium, and large size) and adjacent myometrium identified that ECM-related proteins, including glycoproteins, collagens, and proteoglycans, are upregulated in UFs compared to those in the adjacent myometrium independent of MED12 mutation status. Of these, expression of tenascin C, periostin, collagen type III α-1, collagen type XXIVα-1, and asporin are significantly upregulated even in the small-sized UFs (Jamaluddin et al. 2018a, Jamaluddin et al. 2019, Jamaluddin et al. 2018b). In addition, vitamin D, which can reduce the size of UFs by the inhibition of ECM remodeling, significantly decreased Wnt4, β-catenin, and TGFβ3 expression independent of MED12 mutation status (Corachán et al. 2021). Since Wnt/β-catenin and TGFβ signaling pathways play crucial roles in the formation of ECM in UFs, the MED12 mutation status does not affect ECM remodeling through these pathways. Further studies may be necessary to clarify the impact of MED12 mutations on the maintenance of ECM.

**Role of noncoding RNA in MED12-UFs**

Noncoding RNAs (ncRNAs), classified as long ncRNAs (lncRNAs) that consist of more than 200 nucleotides and small noncoding RNAs (sncRNAs), are aberrantly expressed in UFs (Chuang et al. 2018). The lncRNA, H19, is more highly expressed in UFs than in matched myometrium. H19 promotes the proliferation of UF smooth muscle cells, and the knockdown of H19 in normal human primary uterine smooth muscle cells results in the downregulation of gene expression related to epigenetic regulation, TGF-β signaling, ECM remodeling, and cell growth. In addition, H19 knockdown in primary UF cells and immortalized human UF cell lines decreased the expression of UF-promoting genes, including MED12. H19 expression was positively correlated with MED12 expression. H19 also regulated HMG2A via the H19-let-7 axis. Sex steroids upregulate the expression of the UF-promoting genes in an H19-dependent manner, indicating that H19 may act as an upstream regulator of MED12 and HMG2A (Cao et al. 2019).

The effects of miRNAs in targeting MED12 have been reported. miRNAs are sncRNAs consisting of 18–22 nucleotides that negatively regulate target gene expression by binding to the 3’ untranslated regions of protein-coding transcripts. As a potential mechanism,
ncRNAs competitively bind to the targeted miRNAs by acting as molecular sponges. Overexpression of myocardial infarction-associated transcript (MIAT) has been reported, and higher expression of MIAT has been observed in MED12-UFs than those in wt-UFs. Knockdown of MIAT in UF spheroids decreased mRNA expression of COL1A1, COL3A1, and TGF-β3. MIAT acts as a sponge for the miR-29 family in UFs and may regulate ECM accumulation by regulating the transcription of COL1A1, COL3A1, and TGF-β3 (Chuang et al. 2021).

Furthermore, differential expression of super-enhancer-associated long noncoding RNAs (SE-IncRNAs), a special class of ncRNAs that are transcribed from super-enhancer genomic loci and can activate the expression of nearby genes through various mechanisms, has been reported in UFs compared with myometrial tissues. Differential expression of SE-IncRNAs was observed in the presence of MED12 mutation status, and significantly higher expression of four SE-IncRNAs and their corresponding coding transcripts were observed in MED12-UFs compared to wt-UFs. These differentially expressed SE-IncRNAs may affect the pathogenesis of UFs via their corresponding coding gene expression (Chuang et al. 2022).

Conclusion

Since somatic mutations in MED12 were initially identified in many UFs in 2011, many studies have been conducted to investigate the characteristic difference between MED12-UFs and wt-UFs, the functional role of MED12 mutations, and MED12-mediated signaling pathways for the tumorigenesis of UFs. MED12 mutations observed in UFs not only impair the CDK activity of Mediator but also dysregulate Wnt/β-catenin signaling and other signaling pathways that regulate ECM formation. However, precise mechanisms of how these mutations occur in UFs and how they affect the development and subsequent tumorigenesis of UFs remain still unclear. Further research on the role of MED12 mutations in the pathophysiology of UFs may remove the need for invasive surgical interventions for the treatment of symptomatic UFs in women of reproductive age.

Declaration of interest
The authors declare that they have no competing interests.

Funding
This study is supported by the Japan Society for the Promotion of Science KAKENHI Grants 20K18156 (to YS) and Bayer Academic Support. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements
We would like to thank Editage (www.editage.com) for English language editing.

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Received 6 March 2023
Accepted 5 September 2023
Available online 5 September 2023
Version of Record published 29 September 2023