

# Chromosomal and gene mapping of uterine fibroids: A systematic review

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## Abstract

Genetic mutations and their phenotypic manifestation have been recognized as critical factors in tumorigenesis. However, the relationship between these mutations and the pathogenesis of uterine leiomyomas (UL) remains inadequately characterized. There is compelling evidence to suggest a genetic underpinning in UL development, alongside influences from epigenetics, environmental stimuli, growth hormones, and growth factors. A plethora of studies have tried to elucidate the genetic and epigenetic etiologies associated with UL, but the definitive implications of these findings remain unclear. An extensive systematic review was conducted to investigate the genetic etiologies of UL. This systematic review aimed to consolidate current knowledge on genetic and epigenetic causes of UL, offering a comprehensive perspective on the evidence and its relevance in other solid tumors. A secondary focus was to identify the most significant genetic association with the genesis of UL. A total of 60 articles were identified, and 10 chromosomes and 51 genes were found to be implicated in the development of UL. The main trend in fibroid research focuses on genetic abnormalities and aberrations as the etiology of UL development. It has been estimated that 40% of UL can be associated with chromosome-specific aberrations. Chromosomal gain, loss, rearrangement, single nucleotide polymorphism (SNP), and translocation are the most common aberrations associated with UL development. The most recurrent ones include chromosome X and 7q deletions, and rearrangements of 12q15, 6p21 and 10q22. *MED12* has been identified as a gene of particular importance in the development of UL.

**Key words:** uterine fibroids, tumorigenesis, genotyping, leiomyomas, myoma genetics

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## Highlights

- Systematic review identifies 10 chromosomes and 51 genes implicated in uterine leiomyoma (UL) development, with MED12 as the most critical gene.
- Approximately 40% of UL cases are linked to chromosome-specific aberrations, including gains, losses and translocations.
- Frequent chromosomal abnormalities include X chromosome deletions, 7q loss, and rearrangements of 12q15, 6p21 and 10q22.
- Genetic and epigenetic alterations underscore the complex etiology of UL, offering parallels with mechanisms observed in other solid tumors.

## Introduction

Ontogenetically, the uterus is divided into 2 distinct organs: the inner archimetra and the outer neometra. The archimetra encompasses the endometrium and the subendometrial layer of the myometrium (stratum subvasculare). It is of paramesonephric origin, making it the oldest part of the uterus. The neometra includes the stratum vasculare and the stratum supravasculare of the myometrium, constituting the outer main bulk of the muscular wall.<sup>1</sup>

From an immunocytochemical perspective, the subendometrial layer of the myometrium (stratum vasculare) exhibits a cyclical pattern of estrogen and progesterone (PR) receptor expression, similar to that of the endometrium. In contrast, the outer neometra does not display this cyclical receptor expression. This finding correlates with the functionality of both 'organs,' as the endometrial-subendometrial unit is involved in the cyclical preparation for implantation, while the outer bulk of the uterus requires continuous growth for parturition, necessitating constant exposure to estrogen and PR.<sup>2</sup>

Uterine leiomyomas (UL), also known as uterine fibroids or myomas, are noncancerous growths of the myometrial layer of the uterus. They occur in up to 70% of women, making them the most common reason for gynecologic surgery referrals. Although no single etiology has been identified to directly mediate the development of UL, a multifactorial approach has been adopted to study the causes of these benign masses, with genetics, hormones and growth factors believed to interact in their pathophysiology.<sup>3</sup>

Various attempts to isolate the aberrant genetic etiology of UL have been reported in the literature, leading to numerous associations between chromosomes, genes and their development.

## Objectives

The primary objective of this article was to provide a concise and comprehensive review of the key genetic etiologies involved in the development of UL. The secondary objective was to explore how aberrations in specific chromosome regions might lead to particular pathologies.

## Methods

### Inclusion criteria

Articles were screened based on the following criteria: level of evidence (1–4), focus on leiomyoma, uterine fibroid, or uterine myoma and their genetics, etiology or genomic analysis, and publication in English. Articles were critically analyzed for their reporting of clinical or functional outcomes, as well as clinical follow-up if available. Animal studies, pilot studies and studies with no clear correlation or specific patient outcomes were excluded. Articles related to benign smooth muscle tumors and gastrointestinal stromal tumors (GIST) were also reviewed.

### Search strategy

A comprehensive search for scientific papers reporting genetic etiologies for UL was conducted using the following databases: MEDLINE, PubMed, Embase, Cochrane Library, the American Association for Cancer Research Publications, and the Hunter and Primo search engines of the University of Saint George's (London, UK) and the University of Aberdeen (Aberdeen, UK), respectively. The final list of articles was screened to identify any additional potential sources. Figure 1 illustrates our search strategy as well as the inclusion and exclusion criteria. Our study included all genes found to be associated with UL, and 6 papers focusing on benign smooth muscle tumors were also included. The details of the genes presented in Table 1,2 were retrieved from a total of 60 papers.

### Data analysis

The selected articles were methodically assessed for validity and bias using the Critical Appraisal Skills Program (CASP) to enhance the rigor of this review. The following domains were evaluated to determine whether the criteria were "clearly met", "clearly not met" or "cannot tell" if the criteria were met, where the last option was used for cases the authors could not assess. Randomized controlled trials (RCTs) were appraised using the modified Cochrane scale. This review was conducted

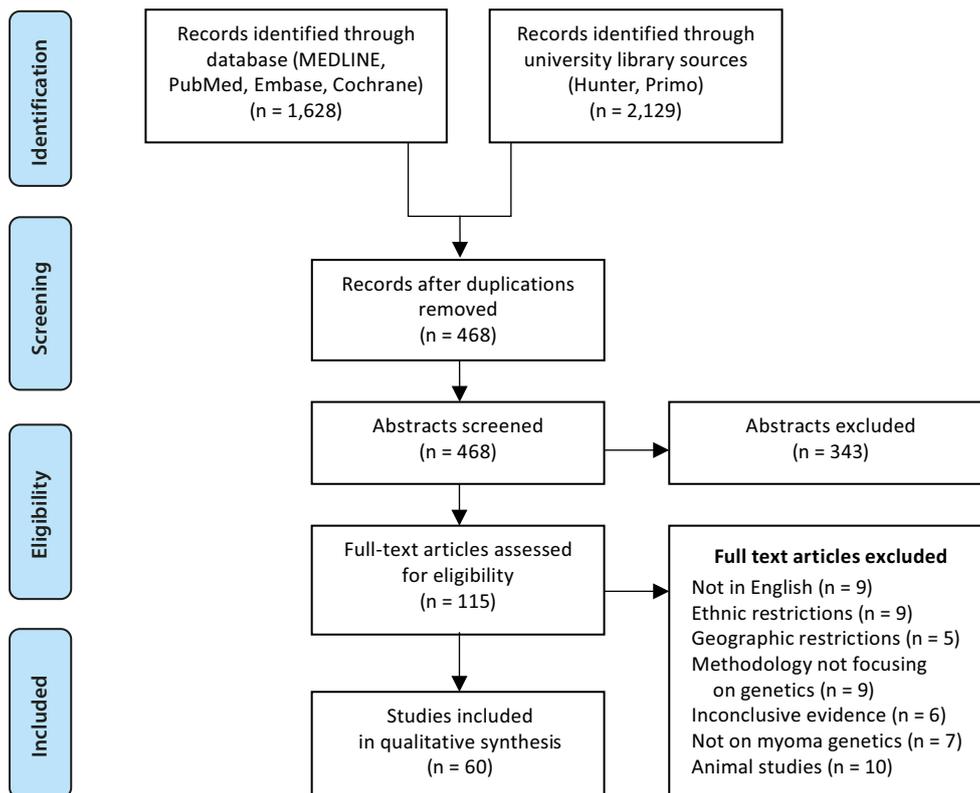


Fig. 1. Flowchart illustrating the search strategy, including inclusion and exclusion criteria

Table 1. Chromosomal localization of genes implicated in uterine leiomyoma<sup>1-50</sup>

Chromosome	Number of genes	Genes involved
1	7	<i>JUN, CSK1, NPHP-4, FH, AJAP1, NPH-4, NCOA1</i>
2	1	<i>NCOA1</i>
3	1	<i>DLEC1</i>
4	2	<i>EG, bFGF</i>
5	2	<i>aFGF, HBEGF</i>
6	4	<i>FKBP5, FYN, HMGA1, EE1</i>
7	8	<i>Activin-A, PDGF, CUX1, CUX1-AGR3, ORCSL, LHFPL3, ZNHIT1, CUL1</i>
9	2	<i>CDKN2A, ENG</i>
10	3	<i>KAT6B, SLK, OBFC1</i>
11	5	<i>BET1L, RIC8A, ODF3, SIRT3, PR</i>
12	4	<i>KRAS, ELK3, HMGA2, IGF-1</i>
14	3	<i>ESR-2, TGF-β, RAD51B</i>
17	2	<i>17B hydroxysteroid, TP53</i>
22	4	<i>PDGFB, TNRC6B, DEPDC5, SMARCB1</i>
X	3	<i>MED12, COL4A5, COL4A6</i>

Table 2. Genetic aberrations identified in genes associated with uterine leiomyoma<sup>1-50</sup>

Aberration	Number of genes	Genes involved
Chromosomal gain	15	<i>JUN, CSK1, EGF, bFGF, aFGF, FYN, HMGA1, ER1, Activin-A, PR, KRAS, ELK3, HMGA2, IGF-1, ESR-2</i>
Chromosomal loss	13	<i>FH, HBEGF, CUX1, ORCSL, LHFPL3, ZNHIT1, CUL1, CDKN2A, ENG, TP53, PDGFB, COL4A5, COL4A6</i>
Single nucleotide polymorphism	11	<i>FH, SLK, OBFC1, BET1L, RIC8A, ODF3, SIRT3, T17B Hydroxysteroid, TNRC6B, DEPDC5, MED12</i>
Translocation	6	<i>NCOA1, AJAP1, NPHP-4, FKBP5, KAT6B, TGF-β</i>
Rearrangement	4	<i>HMGA1, CUX1-AGR3, RAD51B, SMARCB1</i>

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

## Results

In total, 10 chromosomes and 51 genes were involved in UL (Table 1). Five types of aberrations were identified

in 49 of these genes: chromosomal gain, chromosomal loss, rearrangement, single nucleotide polymorphism (SNP), and translocation (Table 2), with chromosomal gain being the most common, appearing in 31% of cases. Although sample frequency could not be compared across studies, the following paragraphs detail the chromosomes and genes most strongly associated with UL development (Supplementary Fig. 1).

### Chromosome 1

Seven genes identified on chromosome 1 have been found to contribute to UL pathogenesis through diverse mechanisms of alteration. Genes involved on the “p”-arm

of chromosome 1 are usually involved in transcription regulation. On the “p”-arm of the chromosome, *JUN*, *AJAP* and *NPHP-4* are located on p21.3-p31.3 and p36 breakpoints, respectively.<sup>4</sup> Genes *AJAP* and *NPHP-4* are usually the translocation partners of *NCOA1* on chromosome 2 (P-24), which is the translocation found to be occurring in 1–3% of UL cases.<sup>4</sup> Additionally, deletions of 1p are observed frequently in UL, and they tend to be associated with distinct histopathological features and possible malignant progression. The gene *KIF1B* is most likely affected with 1p deletions observed in UL.<sup>5</sup>

On the “q”-arm of the chromosome, the genes *CSK1* and *FH* are located at q22 and q43, respectively. The *FH* gene is a tumor suppressor gene (TSG) involved in DNA double-strand break repair,<sup>5</sup> while *CSK1* is a cell cycle regulator. Alterations in the *FH* gene in UL can result from chromosomal loss or a missense mutation,<sup>6</sup> while aberrations in *CSK1* are due to chromosomal gain.<sup>7</sup> Lastly, the 1p13 region of chromosome 1 is subject to epigenetic regulation through hypermethylation in UL and contains the *GSTM5* gene.<sup>8</sup>

## Chromosome 2

On chromosome 2, certain areas have been identified to exhibit epigenetic changes, including *KLF11*, a TSG located on 2p25. *KLF11* is a target of PR and antiprogesterone agents in UL tissues. It is downregulated in UL by repressing most endometrial cytochrome enzymes in Ishikawa cells. *KLF11* binds to the guanine (G) and cytosine (C) DNA sequence (GC) elements of the estrogen-metabolizing enzyme *CYP3A4* promoter, repressing its promoter and enzymatic function. This leads to selective deacetylation of the *CYP3A4* promoter. *KLF11* recruits the coreceptor *SIN3A/HDAC*, and *HDAC* pharmacologically reverses this inhibition.<sup>8</sup>

Furthermore, 2p13, which contains the genes *TET1* and *TET3*, undergoes epigenetic changes in UL. These genes code for an enzyme that regulates DNA methylation. An increase in 5-hmC levels is associated with the up-regulation of *TET1* or *TET3*, leading to transient changes in DNA methylation. This alteration affects the cellular environment and promotes increased proliferation. The suspected association of 2q22.1 with increased tumor size, however, is not linked to the risk of UL.<sup>5</sup>

## Chromosome 3

Insertions, translocations and deletions involving chromosome 3 – such as t(3;7)(p11;p11), ins(2;3)(q31;p12p25) and del(3)(p24) – have been documented in UL, although they are less common compared to other chromosomal abnormalities.<sup>9</sup> Certain regions of the short arm (“p” arm), particularly 3p22, are also subject to epigenetic modifications. This locus includes the *DLEC1* gene, a known TSG. Hypermethylation of *DLEC1* has been implicated in tumorigenesis and has been reported in both esophageal

cancers and UL.<sup>8</sup> Region 3p22 and its adjacent loci are susceptible to various pathogenic mechanisms, including structural alterations and epigenetic silencing.

## Chromosomes 4 and 5

The involvement of growth factors in UL has been mapped to chromosomes 4 and 5. On chromosome 4, *EGF* and *bFGF* are located at q25 and q28, respectively. On chromosome 5, *aFGF* and *HBEGF* are both situated at 5q31.<sup>10</sup> However, to date, no dedicated studies have specifically investigated the frequency or expression levels of *aFGF* and *HBEGF* in this chromosomal region in the context of UL.

*EGF*, *aFGF* and *bFGF* not only share a similar protein size of approx. 100,000–105,000 Da but also exhibit increased expression levels in UL. In contrast, *HBEGF* expression appears to be decreased. Additionally, both *aFGF* and *bFGF* play key roles in promoting angiogenesis, while *EGF* and *HBEGF* primarily contribute to cell proliferation.<sup>11</sup>

The 4q34 region is a site of epigenetic alteration and is associated with the *MORF* gene, which is disrupted by the t(10;17) translocation. This disruption results in a distinct gene expression pattern that is implicated in the pathogenesis of UL.<sup>8</sup>

## Chromosome 6

Chromosome 6 harbors the *HMGAI* and *ESR1* genes, located at positions p22 and q25.1, respectively. Alterations in *HMGAI* often involve gene rearrangements that can lead to its overexpression. Such aberrations have been identified in approx. 3% of UL cases, suggesting a potential, though limited, role in the pathogenesis of these tumors.<sup>5</sup>

However, *HMGAI* aberrations are more commonly secondary changes, with 45-fold increased expression in sample studies.<sup>12</sup> *HMGAI* is important in gene transcription regulation and nucleosome phasing as it regulates genes close or within A+T rich regions.<sup>10</sup> *HMGAI* was also found to be altered in other benign mesenchymal tumors such as lipomas and hamartomas.<sup>5</sup>

Estrogen and PR receptors in UL exhibit cyclical changes similar to those observed in normal uterine tissues during the menstrual cycle. Estrogen levels decrease in the postovulatory phase but remain consistently higher in submucosal compared to subserosal UL, in both the proliferative and secretory phases, paralleling PR levels.<sup>13</sup> In leiomyoma smooth muscle cells, estrogens exert their effects through both estrogen receptor alpha (ER- $\alpha$ ) and beta (ER- $\beta$ ). However, in endothelial and connective tissues, estrogen acts primarily via ER- $\beta$ . Estrogen receptor alpha is expressed exclusively in smooth muscle cells, with its distribution varying across different UL subtypes at the subcellular level. In contrast, ER- $\beta$  is widely distributed across smooth muscle, endothelial and connective tissue cells and is consistently localized within the nucleus. Notably, subcellular variations of ER- $\beta$  expression were observed only in smooth muscle cells.<sup>14</sup>

Estrogen receptor alpha is present in nucleus and cytoplasm, while ER- $\beta$  is localized only in nuclei. Estrogen receptor alpha and ER- $\beta$  proto-oncogenes expressions do not differ between UL and normal myometrium, but in both cases ER- $\alpha$  expression is always higher than ER- $\beta$  expression. Estrogen receptor alpha expression is also higher in both when compared to normal endometrium.<sup>15</sup>

Estrogen receptor alpha mRNA and protein levels in multiple ULs were significantly lower than those in solitary ULs. ER- $\beta$  mRNA and protein levels were significantly higher in multiple ULs than in solitary ones, irrespective of stage of menstrual cycle. In both, ER- $\alpha$  expression was higher than that of ER- $\beta$ . Estrogen receptor alpha concentration was also correlated to E2 concentration in multiple and solitary ULs. Difference in ER- $\alpha$  and ER- $\beta$  expression between multiple and solitary ULs may be responsible for course of disease subtypes.<sup>16</sup> Expression of *IGF-1* mRNA also increases in UL and has been correlated to the upregulation of estrogen by ER-1. The involvement of ER- $\beta$  is also probable but has not yet been found to be statistically significant.<sup>15</sup>

Estrogen receptor alpha to ER- $\beta$  expression ratio rather than individual expression levels can also determine fraction of DNA binding homodimers of ER- $\alpha$ , and possibly the growth potential of myoma.<sup>17,18</sup>

ERs are also found to be changed epigenetically in ULs in different ways. Normally, hypermethylation of the protooncogene at the site 6p21 levels are inversely related to ER expression levels. Hypomethylation to oncogene leads to development of tumorigenesis and ER- $\alpha$  gene, which is highly expressed in UL. Seven CpG sites in distal promoter region of ER- $\alpha$  gene variation were seen compared to normal myometrium. Hypomethylation at this site is correlated with increased ER expression. In addition, *HDAC6* was found to be strongly stained in UL's cytoplasm. Silencing of *HDAC6* by siRNA led to decreased ER- $\alpha$  protein levels but not ER- $\alpha$  mRNA, suggesting that it promoted degradation of ER- $\alpha$  protein in lysosome.<sup>8</sup>

The enzyme 17 $\beta$ -hydroxysteroid dehydrogenase is also altered by polymorphisms in UL, leading to reduced expression. As a result, its substrate, estradiol, accumulates and binds more strongly to ER than its product, estrone.<sup>17</sup> Activation of estradiol further stimulates the pro-mitogenic PI3K/mTOR signaling pathway.<sup>19,20</sup>

## Chromosome 7

Chromosome 7 is implicated in the development of UL, with 5 genes undergoing chromosomal loss: *CUX1*, *ORC5L*, *LHFPL3*, *ZNHIT1*, and *CUL1*. The most recurrent aberration among these involves the *CUX1* gene at locus 7q22.1, with an overall frequency of 14% in all UL.<sup>21</sup>

*CUX1* has a tumor suppressor gene function.<sup>20,21</sup> In UL, *CUX1* chromosomal loss induces a signaling pathway that results in elevated tumor growth and proneness to *PI3K-AKT* repression through transcriptionally downregulating *PIK3IP1* (PI3K inhibitor). Similarly, *CUX1* is a compelling

candidate for the tumor suppressor gene. Its chromosomal loss has been implicated in the development of leukemia and myeloproliferative disorders, where it demonstrated around 45.8% reduction in the expression level.<sup>20</sup> The prevalence of *CUX1* chromosomal loss in hematologic malignancies has been estimated to be 15–25% of acute myeloid leukemias and myelodysplastic syndrome (MDP),<sup>21</sup> and 50% of therapy-related myeloid neoplasms.<sup>20</sup>

On the other hand, *CUX1* can act as a proto-oncogene and contribute to tumor progression<sup>20,21</sup> by resisting apoptosis. It is also involved in the enzyme reaction of the kinases ataxia-telangiectasia mutated (ATM) and ATR (ATM- and Rad3-related) in response to DNA damage.<sup>21</sup>

For instance, a study conducted by Ramdzan et al.<sup>19</sup> showed that 71% of 885 human tumors expressed *CUX1* chromosomal gain. Hence, both decreased and increased expression of *CUX1* can contribute to tumorigenesis by functioning either as a tumor suppressor gene or as oncogene.<sup>21</sup> Finally, *CUX1* was shown to be involved in an inversion-induced fusion chromosomal rearrangement (*CUX1-AGR3*, 7q22-p21) in 1 of the samples.<sup>24</sup>

Located on the same chromosomal locus as *CUX1* at 7q22.1, the *ZNHIT1* gene is found to contribute to UL development in 1 out of 38 samples.<sup>3</sup> The other genes on chromosome 7 that are involved in UL include *ORC5L* on 7q22,<sup>25</sup> *LHFPL3* on 7q22.2-q22.3 (3 out of 4 samples)<sup>26</sup> and *CUL1* on 7q31 (4 out of 38 samples).<sup>3</sup> Nonetheless, it is important to mention that the sample number for the genes *ZNHIT1*, *LHFPL3*, *CUL1*, and *ORC5L* were statistically insignificant and hence their involvement in the pathogenesis of UL cannot be confirmed.

Moreover, the other 2 genes on chromosome 7 are both growth factors and include *PDGFI* on 7p22, and *ACTIVIN-A* on 7p14.<sup>33</sup>

## Chromosome 9

Mehine et al. observed a total of 2 genes on chromosome 9 in 2 out of 6 samples.<sup>31</sup> One such gene is *CDKN2A*, a tumor suppressor located on chromosome 9p21.3, which undergoes chromosomal loss and produces 2 distinct proteins through alternative splicing.<sup>7</sup> The 2<sup>nd</sup> one is concerning a chromosomal loss in *ENG* on 9q33.1-34.2.<sup>7</sup> Epigenetically, the 9q21 region, which contains the *DAPK1* gene, undergoes hypermethylation. *DAPK1*, a TSG, is frequently altered in various human cancers due to its location within a promoter region.<sup>8</sup> Epigenetic changes and chromosomal aberrations at 9p21 and 9p21.3 occur at closely located loci. Further studies are needed to determine whether a correlation exists between them. However, there is no large study sample on chromosome 9 to suggest its significance in UL.

## Chromosome 10 and 11

The *KAT6B* (also known as *MORF*) gene is located on chromosome 10q22. It encodes a histone acetyltransferase

(an enzyme that reduces the affinity of nucleosomes for DNA), thereby enhancing DNA accessibility to transcription factors, i.e., a crucial mechanism in epigenetic regulation. Its most frequent translocation partner is 17q21, a region linked to 17 $\beta$ -hydroxysteroid dehydrogenase. However, the significance of this translocation appears limited, as it has been observed in only 9 out of 171 samples. This suggests it may not be a major event in the studied context.<sup>32,34–36</sup>

Other studied alterations at chromosome 10 are SNP alterations on 10q24.33; the alterations also occur at 11q15.5. 10q24.33 is the location for *SLK* and *OBFC1*, and the 11p15.5 includes *BET1L*, *RIC8A* and *SIRT3*. Most of the genes involved are TSGs and they were observed only in a small sample of patients.<sup>37</sup> The site 10q 25 is found to be altered epigenetically with miR-21. The site contains the *PDCD-4* gene, a tumor suppressor that has been found to be down-regulated in various types of cancer.<sup>8</sup>

## Chromosome 12

A total of 4 genes on chromosome 12 are involved in UL through chromosomal gain. They include *KRAS*,<sup>7</sup> *ELK3*,<sup>7</sup> *HMGA2*,<sup>28</sup> and *IGF-1*.<sup>33</sup> *KRAS* is located on 12p11.22–p13.3 and is a proto-oncogene whose chromosomal gain also leads to non-small cell lung cancer in 30% of the 1.6 million per year lung cancer cases.<sup>34</sup> The other 2 genes (*EKL3* on 12q21.2–q24.3<sup>7</sup> and *HMGA2* on 12q14–15)<sup>28</sup> are both involved in embryogenic development. However, the data samples pertaining to both *KRAS* and *EKL3* are only 3/6 samples,<sup>7</sup> and hence not proven to be significant. Nonetheless, in a study *HMGA2* chromosomal gain was reported in 68/180 samples,<sup>35</sup> which results in upregulation of *IGF2BP2*.<sup>23</sup> The last gene on chromosome 12 to be involved in UL is the growth factor *IGF-1* located on 12q23. This also leads to activation of *IGF-2*, along with *IGF-1*.<sup>33</sup> Moreover, larger fibroids were shown to have elevated *IGF-1* levels in comparison to smaller ones.<sup>33</sup> It is observed from our data that the affected locus of *IGF-1* is within that of *ELK3*, which might encourage more investigations regarding correlation between the 2 genes.

Epigenetics change of the *HMGA2* gene in UL has also been reported. The gene contains structural DNA-binding domains and acts as transcriptional regulation. *let-7* expression is upregulated in UL. It targets *HMGA2*, which is implicated in pathogenesis of mesenchymal tumors like leiomyoma, lipoma and hamartomas.<sup>8</sup>

The dysregulation of *IGF-1* is significantly deregulated in UL. *IGFBP2* is the 2<sup>nd</sup> most expressed gene in the *HMGA2* subtype of UL, as *HMGA2* binds to its AT rich domain and regulates its expression. Subsequently *IGF2BP2* induces the expression of *IGF* mRNA; *IGF* was detected to be upregulated in the majority of *HMGA2* subtypes. *IGF2* is then able to bind to IGF1 receptor and promote growth. Also, *HMGA2*, *IGFBP2* and *IGF2* are

all not expressed in adult tissue, which may indicate they are functionally related. However, *ADAM12* has to be the most uniquely upregulated gene in the *MED 12* subtype, and *PAPPA2* is one among the highest expressed genes in *HMGA2* subtypes. Both genes increase the expression of *IGFBP*, which inhibits the *IGF1* receptor action and inhibits *IGF-1* role in migration and proliferation in smooth muscle. Therefore, the action of *IGFBP5* is still not well understood as to whether it induces or decreases cancer development.<sup>5</sup>

Two genes on chromosome 12 were also relevant to UL genesis, which are *MED12* on Xq13 and *COL4A5/6* on Xq22.3. Chromosomal loss of *COL4A5/6* was observed on 4/38 samples of UL,<sup>21</sup> as well as in Alport syndrome.<sup>20</sup> *MED 12* mutations represent one of the most frequent genetic aberrations to be discovered, accounting to 70% of UL.<sup>36</sup> Along with *HMGA 1&2*, they represent around 80–90%.<sup>6</sup>

Moreover, the mutual exclusivity of *MED12*, *HMGA2*, *FH*, and *COL4A5/6* genetic aberrations was reported.<sup>6</sup> Nonetheless, amongst these cases, up to 60% coexisted with different genetic alterations, including *CUX1* deletions and *HMGA1* mutation.<sup>6</sup> *MED12* mutations also exhibited an increased expression of the gene *RAD51B*.<sup>6</sup> Interestingly, 10–20% of leiomyosarcoma were observed to contain *MED 12* mutations.<sup>20</sup> The malfunction resulting from mutated *MED12* is believed to be caused by an absent transcriptional inhibition affecting cell cycle regulators such as Cdk8 and cyclin C, as well as the WNT signaling pathway.<sup>6</sup> *MED12* engages with *REST* and  $\beta$ -catenin, and both participate in the WNT pathway.<sup>20</sup> This can eventually lead to a decreased expression of *REST*, entailing the upregulation of mTORC.<sup>20</sup>

## Chromosome 14

On chromosome 14, 3 important genes are implicated in UL: *ESR2*, *TGF- $\beta$*  and *RAD51B*. While *ESR2* (also referred to as *ESR-B*) has already been discussed alongside *ESR1* (*ESR-A*), it is worth noting that *ESR2* is located near *TGF- $\beta$*  and *RAD51B* at chromosomal regions 14q22, 14q23–24 and 14q24, respectively.<sup>36</sup> This may require further investigation regarding their association and the frequency of these genetic aberrations occurring together in UL.

In ULs, there is also increased expression of *TGF- $\beta$* ; however, its signaling mechanism remains poorly understood. *TGFB1* is linked to increased expression of fibromodulin, which might lead to fibrotic properties of UL. The expression of *TGFB3* increases the manifestation of extracellular matrix (ECM) components such as *COL1A1* and *FNI*, while decreasing the expression of genes associated with ECM degradation.<sup>37</sup>

*RAD51B* is the preferred translocation partner of *HMGA2*, and this translocation is associated with decreased *HMGA2* expression. However, *HMGA1* and

*HMGA2* rearrangements frequently target other regions in other mesenchymal tumors. Biallelic loss of *RAD51B* was observed in ULs without the involvement of *HMGA2*. The gene encodes a double strand break repair enzyme and may play a role in promoting genomic instability. It is also observed to be uniquely overexpressed in ULs with *MED12* subtypes. However, whether increased expression of this gene is involved in UL development and growth requires further study.<sup>38</sup>

## Chromosome 17

Two genes were reported on chromosome 17. The first one is the TSG *TP53* (located on 17p13.2) that demonstrated chromosomal loss only in 2 out of 6 samples.<sup>7</sup> The 2<sup>nd</sup> genetic aberration is a single nucleotide polymorphism 17 beta-hydroxysteroid, located on 17q21.<sup>17</sup> The site 17q21 is also a site of hypermethylation in ULs. The epigenetic change may involve *KRT19*, another TSG. Hypermethylation can lead to inhibition of the TSG, resulting in tumorigenesis.<sup>8</sup>

## Chromosome 22

The literature identifies a total of 4 genes located on chromosome 22; *PDGFB* on 22q13.1-22q13.3<sup>7</sup> and *TNRC6B* on 22q13.1.<sup>39</sup> *PDGFB* leads to UL development through genetic chromosomal loss and has been reported in 4 out of 6 samples.<sup>7</sup> *PDGFB* mutation can also lead to ovarian cancer.<sup>10</sup> *DEPDC5* is located on chromosome 22q12.2–q12.3 and is implicated in hepatocellular carcinoma.<sup>40</sup> *SMARCB1*, located at 22q11, undergoes rearrangements that can lead to biallelic loss of function, resulting in the inactivation of this TSG.<sup>23</sup>

## Chromosome X

Both the “p”- and “q”-arms of the X chromosome are susceptible to epigenetic modifications, particularly at loci Xp11 and Xq26. In both regions, the predominant alteration observed is DNA hypomethylation. The gene located at Xp11 encodes a cell cycle progression inhibitor, and its reduced expression due to hypomethylation may contribute to tumorigenesis.<sup>8</sup>

## Chromosome 1

The *FH* gene on chromosome 1 is strongly associated with *HLRCC*. However, alterations are observed in only a small subset of UL cases, making its prevalence difficult to quantify.<sup>6</sup> Additional pathologies and malignancies have been related to the *CSK1* and *FH* genes.<sup>26</sup> For instance, while *CSK-1* is implicated in breast, prostate, esophagus, and bladder cancers,<sup>27</sup> *FH* is involved in *HLRCC* and uterine leiomyosarcoma.<sup>6</sup> We examined *JUN* and *CSK-1* genes in 6 samples, with *JUN* showing up in 1 and *CSK-1* in 2

of them.<sup>7</sup> However, a study by Lehtonen et al. reported *FH* aberrations in 5 out of 153 samples.<sup>33</sup>

Similarly, epigenetic regulation also affects some regions of chromosome 1. Uterine leiomyomas involving the *GSTM5* gene are susceptible to hypermethylation at the 1p13 region of chromosome 1. Hypermethylation of this region results in reduced gene expressions, which raises the risk of cancer and exposure to carcinogens.<sup>8</sup> *GSTM5* gene encodes an enzyme involved in the detoxification of electrophilic compounds, including carcinogens.

## Chromosome 2

Regions of chromosome 2 have also been shown to undergo epigenetic alterations. In UL tissues, expression of *KLF11* is reduced, leading to the suppression of several endometrial enzymes.<sup>8</sup> The role of *HDAC* was implicated through *KLF11*'s repression of the *CYP3A4* promoter, and its recruitment of the corepressor complex *SIN3A/HDAC* to mediate this effect.<sup>8</sup> The *TET1/TET3* genes on 2p13 control DNA methylation. An increase in DNA methylation, driven by elevated 5-hmC levels, can influence the cellular environment by promoting cell proliferation. However, the risk of developing UL is not associated with the 2q22.1 region.<sup>8</sup>

## Chromosome 3, 4 and 5

Chromosome 3 insertions, translocations and deletions are consistent but less prevalent in uterine fibroids. 3p22 is the region most frequently affected by epigenetic modification.<sup>9</sup> Hypermethylation of this site contributes to tumorigenesis in UL and esophageal cancers. While *HBEGF* appears to have reduced expression of *EGF*, both *aFGF* and *bFGF* exhibit comparable protein sizes. Both genes contribute to angiogenesis and cell proliferation, and a mutation in the *MORF* gene at 4q34 is associated with a distinct expression pattern involved in the etiology of UL.<sup>8</sup>

## Chromosome 6

*HMGA-1* and *ER-1* genes are found on chromosome 6. The nucleosome-phasing and gene transcription regulatory protein *HMGA1* has been reported to be altered in approx. 3% of uterine fibroids.<sup>11</sup> Both UL and normal myometrium expressed the *ER-α* and *ER-β* proto-oncogenes, with *ER-α* levels being higher than those of *ER-β*. However, multiple UL exhibited significantly lower levels of *ER-α* mRNA and protein compared to single UL. Regardless of the menstrual cycle phase, multiple ULs consistently exhibited significantly higher levels of *ER-β* mRNA and protein compared to solitary ULs.

*IGF-1* mRNA expression is also elevated in UL and has been linked to the increase in estrogen induced by *ER-1*. Beyond individual expression levels, the ratio of *ER-α* to *ER-β* may also predict the proportion of ER-DNA binding as homodimers and, potentially, the myoma's tendency to grow.

Hypermethylation of proto-oncogenes can also lead to epigenetic alterations in ERs. Alterations in the *ER- $\alpha$*  gene have been observed during tumorigenesis, primarily due to hypomethylation of the oncogene when compared to normal myometrium. Additionally, polymorphisms in the 17 $\beta$ -hydroxysteroid dehydrogenase enzyme reduce its expression. This reduction, combined with estradiol activation, can further stimulate the pro-mitogenic PI3K/mTOR signaling pathway.<sup>11</sup>

## Chromosome 7

Seven genes located on chromosome 7 have been associated with the development of UL, with *CUX1* being the most frequently affected. *CUX1* functions primarily as a TSG, and its activation has been shown to inhibit the PI3K-AKT signaling pathway, thereby contributing to tumor progression. Interestingly, *CUX1* also exhibits characteristics of a proto-oncogene, as it can promote tumorigenesis by resisting apoptosis. In addition to its roles in UL, *CUX1* has been implicated in leukemia and myeloproliferative disorders.<sup>20,21</sup> Moreover, it is involved in regulating the enzymatic activity of ATM and ATR kinases, which are critical for the cellular response to DNA damage. In 1 out of 38 UL samples, *ZNHIT1* and *CUL1* were also identified at the same chromosomal locus as *CUX1*. Notably, *CUX1* was found to participate in a chromosomal rearrangement involving an inversion-induced gene fusion.<sup>14</sup>

## Chromosome 9

Two genes located on chromosome 9 – *CDKN2A* (a tumor suppressor gene) and *ENG* – were identified in 2 out of 6 analyzed samples. *ENG* exhibited a chromosomal deletion. Notably, chromosomal abnormalities at loci 9p21 and 9p21.3 occur in proximity, while the *DAPK1* gene, situated at 9q21, is known to be epigenetically susceptible to hypermethylation. Despite these findings, the role of chromosome 9 in UL pathogenesis has not yet been thoroughly investigated in large-scale studies.<sup>8</sup>

## Chromosome 10

*KAT6B*, located on chromosome 10, encodes a histone acetyltransferase that plays a critical role in epigenetic regulation. Several SNPs, including *BET1L*, *RIC8A* and *SIRT3*, have been identified with alterations on 10q24.33 and 11p15.5. Additionally, 10q25 undergoes epigenetic modification involving miR-21. This is associated with the downregulation of *PDCD4*, a gene observed to be suppressed in various malignancies.<sup>16</sup>

## Chromosome 12

Four genes (*KRAS*, *ELK3*, *HMGA2*, and *IGF-1*) have been implicated in UL through chromosomal gain on chromosome 12. *KRAS* is a proto-oncogene known to contribute

to non-small cell lung cancer, while *HMGA2* and *ELK3* are involved in embryonic development. Chromosomal gain of *HMGA2* was detected in 68 out of 180 samples and is known to upregulate *IGF2BP2*. Additionally, studies have shown that larger fibroids tend to express higher levels of the *IGF-1* growth factor.<sup>18</sup>

*IGFBP2* targets *HMGA2*, a gene involved in the etiology of mesenchymal malignancies and the 2<sup>nd</sup> most frequently expressed gene in *HMGA2* subtypes. While *IGFBP2*, *HMGA2* and *IGF2* are generally not expressed in adult tissues, *ADAM12* shows specific upregulation, and *PAPPA2* is identified as the most abundant subtype associated with *HMGA2*. Additionally, *IGF2* can bind to the *IGF-1* receptor, promoting cellular growth.<sup>5</sup>

## MED 12 mutations

The *MED12* and *COL4A5/6* genes also play significant roles in the development of UL. *MED12* mutations represent one of the most common genetic abnormalities in UL, accounting for approx. 70% of UL cases and 80–90% of all UL. These mutations are also associated with increased expression of the *RAD51B* gene. Furthermore, *MED12* mutations have been identified in 10–20% of leiomyosarcomas. Functionally, *MED12* mutations disrupt transcriptional repression, impacting the WNT signaling pathway and key cell cycle regulators. This results in reduced expression of *REST* and increased activity of mTORC, contributing to tumor growth.<sup>27</sup>

## Chromosome 14

The development of UL has also been associated with 3 key genes: *ESR2* (estrogen receptor  $\beta$ ), *TGF- $\beta$*  and *RAD51B*. Although *ESR2* is located in proximity to these genes, its precise role in UL pathogenesis and the frequency of related abnormalities remain unclear. *TGFB3* has been shown to promote the expression of ECM components, including *COL1A1* and *FNI*, while *TGFB1* is associated with increased fibromodulin expression.<sup>10</sup> *HMGA2* frequently selects *RAD51B* as a translocation partner, although *HMGA1* and *HMGA2* rearrangements generally involve distinct genomic regions. *RAD51B*, which encodes a double-strand DNA break repair enzyme, may contribute to genomic instability when disrupted.<sup>5</sup>

## Chromosome 17

One gene located on chromosome 17 – *TP53* (TSG) and 1 enzyme 17 $\beta$ -hydroxysteroid dehydrogenase – have been implicated in the pathogenesis of UL. *TP53* exhibits chromosomal loss in 2 out of 6 analyzed samples, while 17 $\beta$ -hydroxysteroid dehydrogenase is frequently hypermethylated in UL tissues. Such hypermethylation may suppress TSG activity, thereby contributing to tumor development. Furthermore, the involvement of estrogen signaling and the KRT19 pathway has also been suggested.<sup>24</sup>

## Chromosome 22

Our research identified 4 genes located in close proximity on chromosome 22, including *PDGFB* and *TNRC6B*. Overexpression of *PDGFB* has been associated with the development of ULs, and mutations in this gene have also been linked to ovarian cancer. *DEPDC5* has been reported to harbor a truncating mutation, while *SMARCB1* exhibits a rearrangement that results in the biallelic loss of its tumor suppressor function.<sup>25</sup>

## Chromosome X

The Xp11 and Xq26 regions of the X chromosome are particularly susceptible to hypomethylation-related epigenetic alterations, which may contribute to tumorigenesis.<sup>8</sup>

## Discussion

A multifaceted approach has been employed to investigate the causes of UL, focusing on the interplay between genetics, hormones and growth factors (GFs) in their pathophysiology.<sup>25</sup> Multiple attempts have been made to identify the abnormal genetic etiology of UL. Genetic abnormalities and aberrations are the primary focus of fibroid research as an explanation for their emergence. Chromosomal gains, losses, rearrangements, SNPs, and translocations are the most common genetic aberrations associated with the development of UL. Among these, deletions on chromosome X and 7q, as well as rearrangements of 12q15, 6p21 and 10q22, are the most frequent.<sup>28</sup>

The relevance of genetics in UL is based on several key principles: risk assessment, early disease detection, personalized treatment approaches, fertility counseling, prognosis, and research. High-risk patients, particularly those with a personal or family history of UL and those of African descent, may benefit from early detection and management. This proactive approach can help minimize the risks associated with delayed or complicated surgeries and support fertility-sparing treatments. Additionally, genetic information can guide treatment decisions, including the selection of personalized therapies and influencing responses to certain medications. Prognostic information regarding the behavior and progression of UL can help guide clinicians and patients in making informed decisions about management and treatment options. Lastly, understanding the genetic basis of UL can drive further research into their underlying causes, molecular mechanisms and the development of potential targeted therapies.

The significance of epigenetics in the formation of ULs is still being investigated, and the literature does not yet fully characterize this involvement. The interaction between genetics and epigenetics may help explain why

certain genes and phenotypes are more prevalent in UL. Numerous alterations appear to occur at chromosomal loci strongly associated with their development. Other loci, including proto-oncogenes, growth factors and TSGs, have also been shown to undergo several epigenetic modifications.<sup>12</sup> For each type of modification, epigenetics must be further studied in terms of statistical significance and population samples. Lastly, further research is needed to determine how changes in the size and architecture of UL are related to these investigations.

## Limitations of the study

Not all of the analyzed studies reported sample sizes used to establish genetic associations, leading to inconsistencies across the literature. This heterogeneity limited the ability to directly compare the frequency of genetic variants between studies. As a result, it was not possible to categorize the studies based on the strength or quality of the evidence they provided.

## Conclusions

The predominant focus in UL research has been on genetic abnormalities and chromosomal aberrations as key factors in the disease's etiology. It is estimated that approx. 40% of UL cases are associated with chromosome-specific alterations. The most commonly reported aberrations include chromosomal gains, losses, rearrangements, SNPs, and translocations. Among these, deletions on chromosome X and 7q, as well as rearrangements involving 12q15, 6p21 and 10q22, are the most recurrent. One gene that has emerged as particularly significant in the pathogenesis of UL is *MED12*, which has been frequently implicated in tumor development. However, inconsistencies across studies limit the ability to directly compare genetic associations, warranting cautious interpretation of the findings.

## Supplementary data

The supplementary materials are available at <https://doi.org/10.5281/zenodo.17223641>. The package contains the following files:

Supplementary Fig. 1. Genes most strongly associated with the pathogenesis of ULs.

## Use of AI and AI-assisted technologies

Not applicable.

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