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GENETIC AND BIOMARKER PERSPECTIVES ON UTERINE FIBROIDS: A REVIEW OF EMERGING MOLECULAR INSIGHTS

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ABSTRACT

Up to 70% of women worldwide suffer from uterine fibroids, also known as leiomyomas, which are benign monoclonal tumors originating from the uterine smooth muscle. They can result in infertility, irregular uterine bleeding, and lower quality of life, despite often being asymptomatic. Previously thought to be primarily caused by hormonal imbalances, fibroids are now understood as complex conditions impacted by environmental, genetic, and epigenetic factors. Recent developments in their molecular landscape are summarized in this review, with special attention to driver mutations like *MED12*, *HMGA2* overexpression, *FH* loss, and chromosomal rearrangements. We discuss the "two-hit hypothesis," which holds that myometrial stem cells are primed for tumorigenesis after somatic mutations due to early exposure to endocrine-disrupting chemicals. The role of epigenetic changes and ethnic differences in disease heterogeneity is investigated. Biomarkers such as matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), extracellular matrix proteins, circulating microRNAs, *MED12*-mutant DNA fragments, and vitamin D are discussed in relation to diagnosis, prognosis, and therapeutic targeting. Proteomic profiling and liquid biopsy are examples of novel techniques investigated. The paper concludes by emphasizing integration of molecular diagnostics and personalized

medicine into routine fibroid care, enabling precise, less invasive management through combined genomic, epigenomic, and biomarker data.

KEYWORDS: Uterine fibroids, MED12 mutation, HMGA2, matrix metalloproteinases (MMPs), endocrine-disrupting chemicals, personalized medicine.

1. INTRODUCTION

Uterine fibroids are among the most prevalent gynecological tumors, especially in women of reproductive age. They are non-malignant but can lead to symptoms like menorrhagia, pelvic pressure, infertility, and recurrent pregnancy loss. The economic and health burden of fibroids is considerable, with annual healthcare costs in the U.S alone reaching $34 billion.[1] Despite their prevalence, the pathogenesis of fibroids remains incompletely understood, and current treatments are often invasive or temporary. Advances in molecular biology, particularly genetics and biomarker research, provide new insights into fibroid biology and open up opportunities for precision medicine. Recent epidemiological studies suggest that up to 70% of women may develop fibroids by the age of 50, with African American women disproportionately affected in both incidence and severity.[2,3] These tumors display a range of growth patterns, hormone sensitivities, and extracellular matrix compositions, underscoring their biological heterogeneity. Historically, fibroids were managed surgically through hysterectomy or myomectomy, but recent years have seen a shift toward uterine-sparing, medical, and minimally invasive interventions. However, many of these therapies offer only temporary relief and may not be suitable for all patients, particularly those with multiple or large tumors.[4-6]

Understanding the genetic and molecular underpinnings of fibroid development is therefore essential. Discoveries in genomics and transcriptomics have identified several recurrent mutations and disrupted signaling pathways, most notably involving the MED12 gene. Moreover, environmental exposures, especially endocrine-disrupting chemicals, are now recognized as contributing to fibroid susceptibility through epigenetic mechanisms. The integration of this molecular knowledge with biomarker science holds promises for advancing early diagnosis, monitoring disease progression, and personalizing treatment.[7]

Uterine fibroids (leiomyomas) are benign monoclonal neoplasms originating from the smooth muscle layer of the uterus and affect up to 70% of women globally. Although often asymptomatic, they can cause significant reproductive and quality-of-life issues. Recent

molecular research has shed light on their developmental origins, genetic mutations, and potential biomarkers, thereby offering promising avenues for diagnosis and targeted therapies.[8] This review focuses on the genetic landscape and biomarker discoveries relevant to uterine fibroids, drawing on evidence from recent high-impact studies. Particular emphasis is placed on MED12 mutations, HMGA2 overexpression, and the role of matrix metalloproteinases (MMPs) in fibroid development and progression. A detailed literature review and an expanded biomarker analysis are included to strengthen the understanding of molecular diagnostics.

2. LITERATURE REVIEW

Uterine fibroids have been the subject of extensive investigation over the past two decades, yet their underlying etiology and progression mechanisms remain partially elusive. Key historical studies identified the monoclonal nature of fibroids and hormonal regulation, particularly by estrogen and progesterone.[9,10] Early histopathological analyses distinguished fibroids from sarcomas and emphasized the dense ECM composition, later corroborated by molecular and immunohistochemical studies.[11] A major breakthrough occurred in the early 2010s when MED12 mutations were discovered in the majority of fibroids, establishing a genetic basis for these tumors. Yang et al. (2021) consolidated findings on fibroid genomics, epigenetics, and clinical behavior, highlighting the complexity and heterogeneity of the disease. Simultaneously, fibroid classification systems evolved to include molecular signatures alongside anatomical location (e.g., FIGO classification).[11-13]

The understanding of the fibroid microenvironment advanced with studies demonstrating an overproduction of collagen types I and III, driven by TGF-β and influenced by MMP/TIMP imbalance. Transcriptomic and proteomic studies subsequently revealed enrichment of inflammation, angiogenesis, and ECM remodeling pathways in fibroid tissues compared to normal myometrium.[14,15] More recently, liquid biopsy approaches and single-cell RNA sequencing have provided insights into cellular heterogeneity within fibroids, identifying tumor-initiating stem cells and subpopulations responsive to hormonal signalling.[16]

From a clinical standpoint, research has shifted toward identifying non-invasive diagnostic biomarkers and therapeutic targets to reduce reliance on surgery. Studies investigating vitamin D supplementation, GnRH antagonists, selective progesterone receptor modulators (SPRMs), and anti-fibrotic agents such as pirfenidone and simtuzumab reflect this translational push.[17] The integration of genetic profiling into clinical workflows remains

limited but is anticipated to increase with improved accessibility to high-throughput sequencing. Together, these studies form a robust foundation for current and future research into the pathogenesis, diagnosis, and management of uterine fibroids, emphasizing the value of biomarker discovery in moving toward personalized, less invasive care.[17,18] Figure 1 illustrates the major genetic subtypes of uterine fibroids. These genetic pathways are visualized in relation to fibroid formation.

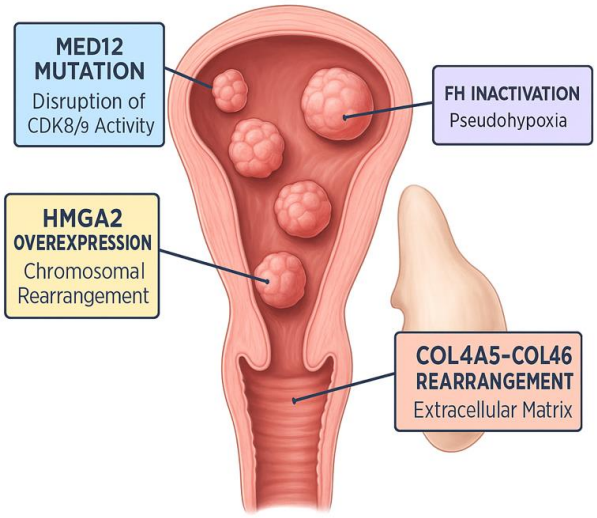

Figure 1: Diagram of Genetic Alterations in Uterine Fibroids.[19]

3. LANDSCAPE OF UTERINE FIBROIDS

MED12 Mutations MED12 (Mediator Complex Subunit 12) mutations are the most common genetic aberrations in uterine fibroids, present in up to 90% of cases, depending on the population. These mutations are primarily localized in exon 2 and disrupt the CDK8/19 kinase activity, which is essential for proper transcriptional regulation. Functional studies have demonstrated that MED12 mutations can independently induce fibroid formation in murine models, confirming their pathogenic role.[11]

Other Genetic Alterations Aside from MED12, several other driver mutations have been implicated in fibroid development:

HMGA2 Overexpression: This chromatin-associated protein is involved in growth regulation. Its overexpression, often due to chromosomal rearrangements, is linked to fibroid formation and seen in fibroids lacking MED12 mutations.[11]

FH (Fumarate Hydratase) Mutations: Biallelic loss of FH leads to metabolic dysregulation and pseudohypoxia, contributing to tumorigenesis and typically associated with hereditary leiomyomatosis.[11]

COL4A5-COL4A6 Rearrangements and Chromosomal Aberrations: These include alterations in chromosomes 6p21, 7q22, 22q, and 1p, often co-occurring with other mutations and affecting ECM-related pathways and cellular signalling.[11]

Ethnic and Epigenetic Considerations: African American women are disproportionately affected by fibroids, both in terms of incidence and severity. This disparity is partially attributed to higher MED12 mutation frequency, vitamin D deficiency, and possible epigenetic reprogramming of myometrial stem cells by early-life exposures, including endocrine-disrupting chemicals (EDCs).[11]

Epigenetics and Tumor Initiation: Recent models suggest a two-hit hypothesis where early exposure to EDCs causes epigenetic reprogramming of myometrial stem cells, which are later transformed into tumor-initiating cells by genetic mutations such as MED12. This process involves aberrant cell proliferation, ECM accumulation, and DNA instability, suggesting a convergence of genetic and epigenetic mechanisms in fibroid pathogenesis.[11,19] The following table summarizes key genetic mutations associated with uterine fibroids, highlighting their mechanisms and clinical relevance.

Table 1: Summary of Major Genetic Mutations in Uterine Fibroids.[20]

Gene	Frequency	Mechanism	Clinical Relevance
MED12	70–90%	Disruption of CDK8/19	Smaller tumor size, multiple tumors
HMGA2	~10–15%	Chromatin remodeling	Large solitary tumors
FH	Rare	Metabolic reprogramming	Associated with syndromic cases

4. BIOMARKERS IN UTERINE FIBROIDS

Matrix Metalloproteinases (MMPs) are zinc-dependent endopeptidases critical for the turnover of ECM components. Dysregulation of MMPs contributes to aberrant ECM accumulation seen in fibroid pathophysiology. Although MMPs have been extensively studied in hepatic fibrosis and cancer, their role in uterine fibroids is gaining attention due to the shared mechanism of fibrosis-like ECM deposition.[5,20,21]

MMP-2 and MMP-9, gelatinases that degrade denatured collagen and fibronectin, are consistently found to be upregulated in fibroid tissue. This upregulation is often accompanied

by increased tissue stiffness, suggesting MMP-mediated ECM remodeling paradoxically promotes further fibrotic changes via disrupted feedback signalling.[5,21]

MMP-1, a collagenase targeting fibrillar collagens (types I and III), is typically downregulated in fibroids. This imbalance, coupled with high levels of TIMP-1 and TIMP-2, favors ECM preservation and contributes to tumor rigidity. These markers also exhibit hormonal responsiveness, with higher progesterone levels correlating with suppressed MMP expression and enhanced ECM accumulation.[22,23] Further studies have investigated MMP-7, -13, and -14, showing variable expression levels depending on fibroid subtype and phase of menstrual cycle. Importantly, the MMP-2: TIMP-2 ratio has emerged as a dynamic indicator of active ECM remodeling and may serve as a potential serum biomarker for disease monitoring.[24,25]

Immunohistochemistry and zymography analyses support these findings, demonstrating altered MMP localization and activity patterns in fibroid tissues compared to adjacent normal myometrium. These observations lay the groundwork for MMPs to be used as diagnostic and prognostic markers and, potentially, as therapeutic targets using MMP inhibitors or activators.[23,26]

ECM Components and Associated Proteins: The ECM of fibroids is not only abundant but biochemically distinct. It includes collagens (types I, III, V), elastin, fibronectin, versican, biglycan, and decorin. The abnormal accumulation of these proteins disrupts mechanical signaling and contributes to hormonal resistance. Notably, fibronectin and versican levels have been correlated with fibroid size and symptom severity.[5,21]

TGF-β, a cytokine that stimulates collagen synthesis and inhibits MMP activity, is overexpressed in fibroid tissue and acts as a central regulator of ECM expansion. Several downstream effectors of TGF-β, such as SMAD2/3 and PAI-1, are also upregulated and contribute to fibrosis.[27]

Serum levels of ECM-related proteins, including procollagen type III N-terminal peptide (PIIINP) and glycosaminoglycans, are being explored as biomarkers. However, most data remain preliminary and require validation in larger cohorts.[28] Table 2 provides an overview of selected MMPs implicated in fibroid ECM remodeling, their functional roles, and diagnostic significance.

Table 2: MMPs in Fibroid Pathogenesis.[29,30]

MMP	Expression in Fibroids	Function	Diagnostic Potential
MMP-1	Decreased	Collagen I degradation	Inversely correlated with severity
MMP-2/9	Increased	ECM remodeling	Candidate for blood-based tests
MMP-14	Variable	Membrane remodeling	Regulates local invasion

Circulating Molecular Markers Circulating biomarkers offer a non-invasive alternative for diagnosis and monitoring. Among these:

microRNAs (miRNAs): miR-21, miR-29, miR-200c, and miR-93 are differentially expressed in fibroid tissue and plasma. These miRNAs regulate fibrogenic pathways and may distinguish fibroid patients from controls.[5,31]

Circulating tumor DNA (ctDNA): Fragments harboring MED12 mutations have been detected in plasma, offering a liquid biopsy approach for fibroid detection.[12]

Vitamin D levels: Low serum 25(OH)D levels are associated with increased fibroid risk and size. Vitamin D downregulates TGF-β, MMPs, and proliferative markers in fibroid cells, suggesting it may act as both a biomarker and therapeutic agent.[32,33]

Proteomic markers: Emerging studies using mass spectrometry have identified proteins such as annexin A2, heat shock proteins, and cytokeratins in fibroid serum samples. These may serve as novel biomarker candidates with diagnostic specificity.[34]

Altogether, these findings reflect a growing toolkit of potential biomarkers spanning genetic, proteomic, and epigenetic domains. Systematic validation and standardization are needed before integration into clinical practice. Figure 2 presents the two-hit hypothesis of fibroid pathogenesis, demonstrating how early epigenetic reprogramming and later somatic mutations (e.g., MED12) lead to tumor initiation.

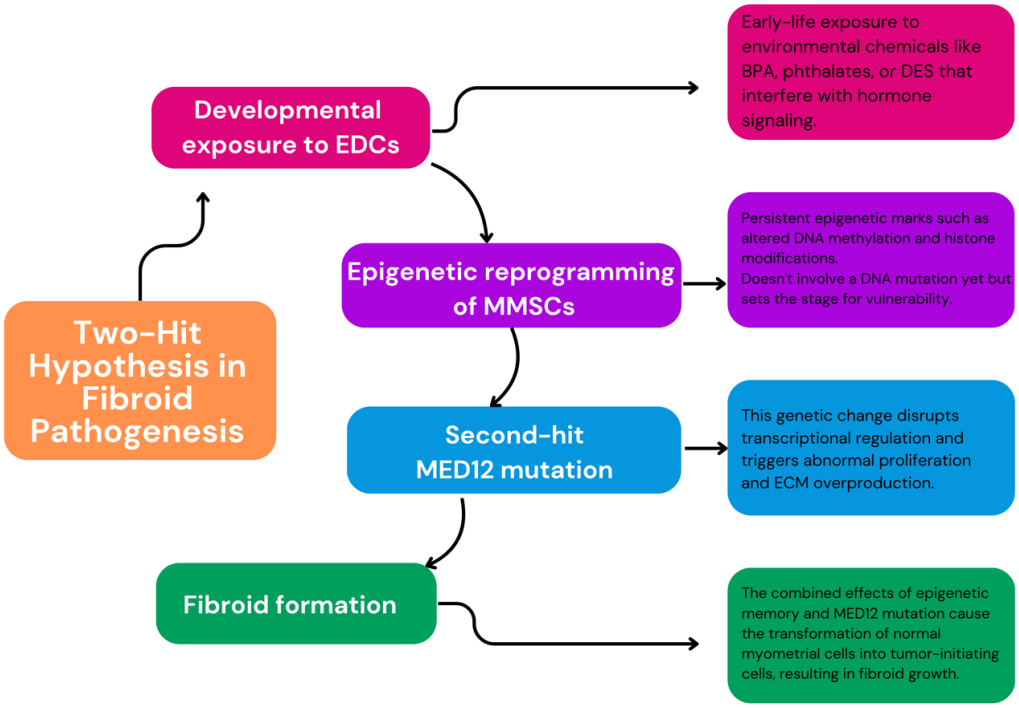

Figure 2: Two-Hit Hypothesis in Fibroid Pathogenesis.[35]

5. DISCUSSION

Recent decades have witnessed major progress in unraveling the molecular biology of uterine fibroids, yet translational application remains nascent. The discovery of MED12 exon 2 mutations as a dominant genetic alteration has catalyzed research into mutation-driven tumorigenesis.[36] These mutations affect transcriptional regulation via Mediator-CDK8/19 dysfunction and exhibit differential prevalence across ethnicities. While some fibroids harbor alternative drivers such as HMGA2 or FH mutations, MED12 mutations remain the most tractable target for molecular diagnostics.[12,37]

Epigenetic reprogramming—particularly of myometrial stem cells exposed to EDCs—suggests fibroids may originate through a developmental misstep. This hypothesis is supported by observations of altered chromatin regulation and the persistent activation of growth and ECM deposition pathways. Integration of these findings underscores the multifactorial etiology involving genetics, epigenetics, and environmental influences.[38,39]

MMPs emerge as compelling biomarkers due to their active role in ECM remodeling. Although primarily studied in hepatic fibrosis, MMP dysregulation in fibroids mirrors that of fibrotic tissues elsewhere.[40] Reduced MMP-1 and increased MMP-2/-9 levels reflect active-matrix deposition over degradation, aligning with fibroid stiffness and growth. Furthermore,

the reciprocal relationship between MMPs and TIMPs offers a regulatory framework that could be exploited therapeutically.[21,41,42]

Vitamin D also stands out as a modifiable systemic factor with biomarker and therapeutic implications. Epidemiological studies correlate deficiency with fibroid burden, and in vitro models show that vitamin D modulates genes regulating inflammation, growth, and ECM composition. This highlights potential for nutritional intervention in high-risk populations.[33,43]

Despite these advances, several challenges persist. There is a lack of large-scale, prospective biomarker validation studies.[44] Many candidate markers, including MMPs and circulating miRNAs, lack standardization in measurement protocols. Moreover, multi-omics integration—combining genomics, transcriptomics, and proteomics remains limited in fibroid research.[45,46]

Moving forward, precision medicine for fibroids will require harmonized efforts across molecular research, biomarker discovery, and clinical trial design. Genetic stratification based on driver mutations should guide enrollment and response monitoring in interventional studies. Liquid biopsy approaches, including circulating mutant DNA or miRNAs, could revolutionize diagnosis and surveillance. Finally, deeper insight into tumor microenvironment including immune cell infiltration and fibroblast activation will be crucial to develop holistic, systems-level interventions.

6. CONCLUSION

Uterine fibroids, though benign in nature, represent a major gynecological challenge due to their high prevalence, variable symptomatology, and complex pathogenesis. Historically viewed as hormonally driven growths, our evolving understanding of fibroids reveals a nuanced interplay of genetic, epigenetic, and environmental factors. This complexity underscores the need for multi-dimensional diagnostic and therapeutic approaches beyond traditional surgical methods.

From a genetic standpoint, the identification of MED12 mutations as a dominant driver has been transformative. These mutations, found in the majority of fibroids, affect critical transcriptional machinery and signal a shift from broad empirical understanding to precise molecular classification. Coupled with findings on HMGA2 overexpression, FH loss, and

chromosomal rearrangements, we now recognize distinct molecular subtypes of fibroids, each with unique pathogenic and clinical implications. Importantly, this genotypic diversity mandates individualized diagnostic tools and therapeutic strategies.

Epigenetic influences, particularly those stemming from early-life exposure to endocrine-disrupting chemicals, have emerged as a crucial predisposing factor. The two-hit hypothesis of fibroid formation—wherein developmental reprogramming of myometrial stem cells is followed by somatic mutations—provides a powerful explanatory model. This underscores the role of environmental and developmental biology in gynecologic disease and opens avenues for early preventive interventions.

The role of biomarkers in fibroid detection and monitoring is an expanding field that bridges molecular pathology and clinical care. Matrix metalloproteinases (MMPs), especially MMP-1, MMP-2, and MMP-9, have shown promise in reflecting fibroid-associated extracellular matrix remodeling. These enzymes, together with their inhibitors (TIMPs), may eventually serve as non-invasive indicators of fibroid activity or response to therapy. Similarly, the potential of circulating markers—such as microRNAs, MED12-mutant DNA fragments, and vitamin D levels—represents a step toward minimally invasive, personalized medicine.

Despite these advancements, challenges remain. Current biomarker candidates lack standardization and require large-scale validation. The incorporation of fibroid-specific molecular profiling in routine clinical practice is limited by cost, accessibility, and infrastructure constraints. Nonetheless, research trends point to a future in which fibroid diagnosis and management are guided by a combination of imaging, genomics, proteomics, and bioinformatics.

Therapeutically, the translation of molecular findings into targeted interventions is in its infancy. Agents modulating ECM turnover, MMP activity, or hormone responsiveness could complement existing treatments. Vitamin D supplementation and MMP modulators represent low-cost, accessible strategies pending further validation. Moreover, the development of liquid biopsy technologies offers a promising frontier for diagnosis, risk stratification, and surveillance.

In conclusion, the integration of genetic and biomarker insights into fibroid research has significantly advanced our understanding of this common condition. The convergence of

genomics, molecular biology, and clinical research holds great promise for developing personalized, effective, and less invasive treatment strategies. Future research should aim to bridge gaps between bench and bedside through robust clinical trials, longitudinal biomarker studies, and equitable access to molecular diagnostics. By embracing a systems-level view of fibroid biology, we can move toward a future where treatment is tailored not just to symptoms, but to the molecular signature of the disease itself.

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Conflict of Interest

None.

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