A simplistic approach to fibroids is outdated

With the advances in genomic sequencing and the frequent emergence of new information, it is no longer possible to take a simplistic approach to fibroids. Fibroids, also known as uterine leiomyomas, are composed of myofibroblasts encased in a prominent extracellular matrix. Fibroids have been observed in approximately 80% of Black women and almost 70% of White women by the age of 50 (1) and represent a substantial health burden for millions of women. Despite their prevalence, the exact molecular mechanisms responsible for this common condition remain unknown. Recently, however, genome-wide sequencing has expanded our understanding of the genetic alterations, both acquired and inherited, that contribute to the development of fibroids, bringing us closer to an explanation of their formation and growth.

Not all fibroids are the same. Fibroids may be subdivided into two broad categories. The first is the common variety frequently encountered in the general population, which is associated with acquired somatic chromosomal mutations. The second category is composted of rarer syndromic types that may be associated with germline mutations. The more common type has been linked to somatic mutations within these fibroids that are thought to perpetuate tumor development and growth. Genomic sequencing has revealed changes in several specific genes (2) such as MED12 and HMGA2, which have been observed in 80%–90% of common fibroids. Despite the absence of known germline mutations, a high degree of heritability has been demonstrated by twin studies and the racial differences apparent in the commonly encountered variety of fibroids. Fibroids in Black women typically present earlier, are more numerous, and are often larger in size. Conversely, fibroids among White women typically arise later in life, with fewer and smaller fibroids (1). Genetic, environmental, and epigenetic factors have been proposed to account for the different phenotypes observed. Proteogenomic analysis comparing fibroids between White and Black women suggest differences in the molecular underpinnings between races (3, 4). A single nucleotide polymorphism, rs57542984, was found to be associated with maximal fibroid dimension, and the effect allele was only present in Black women. Two other single nucleotide polymorphisms have been linked to fibroid volume, rs10024805, and rs6605005, with the former more frequently observed in Black women and the latter in White women (3). These associations reinforce the genetic influence within the common variety of clinically encountered fibroids.

The second broad category may be designated as syndromic fibroids. Such tumors develop as a result of germline mutations or heritable changes in DNA. To date, the most recognized genetic syndrome associated with the development of fibroids is hereditary leiomyomatosis and renal cell cancer (HLRCC). It is caused by a heterozygous germline mutation in the fumarate hydratase (FH) gene. The condition affects >200 families, with an estimated prevalence of 1/10,000–50,000. Fumarate hydratase is a key enzyme in the Krebs cycle, catalyzing the conversion of fumarate to malate. In the absence of FH, fumarate accumulates in cells and subsequently modifies cysteine residues to S-(2-succino) cysteine (2-SC). This succination and the buildup of fumarate are both thought to contribute to dysregulated cell metabolism and DNA damage in individuals with germline FH mutations. This dysregulation of cellular processes is understood to lead to tumorigenesis (4). Hence, HLRCC is associated with an increased risk of cutaneous leiomyomas, fibroids, and renal cell carcinoma.

Another hereditary syndrome is Alport syndrome and diffuse leiomyomatosis, which results from deletions affecting collagen genes COL4A5 and COL4A6 (2). Features of this syndrome include sensorineural deafness and diffuse leiomyomatosis of the tracheobronchial, esophageal, and genitourinary tract. Genome-wide association studies have also identified other variants in the human genome associated with the development of fibroids in the analyzed population groups. In the future, we expect that additional syndromic diseases featuring uterine fibroids will be recognized. In some cases, these mutations may be associated with other conditions, including cancer predilection, as for HLRCC.

It is important for clinicians to recognize the heritable causes of fibroids. This is especially vital in cases of HLRCC, as illustrated brilliantly by the case report published in this issue of the journal (5). Renal cell carcinomas that develop in patients harboring HLRCC mutation are aggressive and carry a poor prognosis. Hence, early diagnosis is paramount to facilitate timely screening for cancer in patients and their affected family members. Clinicians must rely on a thorough history and physical examination to aid in the diagnosis of HLRCC. A detailed history, including a personal or family history of cutaneous lesions, renal tumors, or early presentations with fibroids, is vital to ascertain. The examination should include assessment for skin lesions, especially in very young women with symptomatic fibroids, to ensure that an opportunity for early diagnosis is not missed. These lesions are the size of a common nevus but instead appear as hard areas within the skin that can be painful or recognized by the patient.

Certain immunohistochemistry findings, morphological features, and magnetic resonance imaging findings have been observed in fibroids from patients with HLRCC. Morphological features described in these fibroids include increased cellularity, prominent eosinophilic nucleoli with perinucleolar halos, hyaline globules, and staghorn vasculature (5). Furthermore, there are two immunohistochemistry targets to aid in the identification of these fibroids. The first is FH staining, with most fibroids from patients with HLRCC demonstrating a loss of FH staining because of germline FH mutations (5). Another potential marker is 2-SC, which accumulates in FH-deficient fibroids, resulting in a positive 2-SC stain on immunohistochemistry (4). Although FH-deficient fibroids are also seen in the general population because of somatic FH mutations, these histologic findings can still raise

suspicion of HLRCC and lead to further investigation if clinically warranted. On imaging, we have observed that the HLRCC fibroids may display a hyperintense signal on T2-weighted magnetic resonance imaging. This finding can help to distinguish between HLRCC-caused tumors and common fibroids in a single scan. The presence of these imaging or histologic features, when corroborated with a patient's history, can prompt genetic analysis to substantiate the diagnosis of HLRCC.

In conclusion, although syndromic fibroids currently make up a small proportion of uterine fibroids, their identification is paramount. Clinicians must apply their clinical acumen to facilitate the timely identification of these patients with hereditary fibroids. Furthermore, certain imaging and immunohistologic findings could aid in affirming a clinical suspicion and prompt further genetic testing. Perhaps, with the continued identification of various genetic mutations and polymorphisms associated with fibroids, future screening may include genomic analysis. Furthermore, a greater understanding of the genetic influences on the development and growth of fibroids could also allow for the development of more targeted therapies in the future.

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REFERENCES

1. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in Black and White women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
2. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers 2016;2:16043.
3. Bray MJ, Wellons MF, Jones SH, Torstenson ES, Edwards TL, Velez Edwards DR. Transethnic and race-stratified genome-wide association study of fibroid characteristics in African American and European American women. Fertil Steril 2018;110:737–45.e34.
4. Bateman NW, Tarney CM, Abulez T, Soltis AR, Zhou M, Conrads K, et al. Proteogenomic landscape of uterine leiomyomas from hereditary leiomyomatosis and renal cell cancer patients. Sci Rep 2021;11:9371.
5. Rivera-Cruz G, Boyraz B, Petrozza JC. How a woman's myomectomy saved her father's life: evidence of fumarate hydratase–deficient uterine leiomyoma and early detection of germline variants in fumarate hydratase. Fertil Steril 2022;3:26–31.