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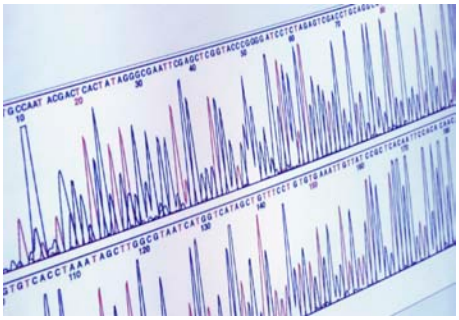
## Leiomyoma

**Major finding:** *MED12* is mutated in 70% of uterine leiomyomas (fibroids).

**Impact:** The Mediator kinase module is implicated in the genesis of multiple types of neoplasms.

**Mechanism:** Heterozygous *MED12* mutations predominantly occur in the expressed X chromosome.

### *MED12* MUTATIONS ARE PRESENT IN THE MAJORITY OF UTERINE LEIOMYOMAS



Leiomyomas, or benign fibroids of the uterine wall, occur in more than half of all women over age 45 and can cause pain, abnormal bleeding, and infertility. Mäkinen and colleagues sequenced the exomes of 18 uterine leiomyomas and matched normal tissue to better understand the genetic basis of this tumor. The most frequent genetic alteration observed was in the *Mediator complex subunit 12* (*MED12*) gene on chromosome Xq13.1. MED12 is a subunit of the Mediator transcriptional adapter complex, a molecular bridge between the basal transcriptional machinery and its upstream activators. MED12 is one of 26 subunits of this complex and part of the "kinase" module, together with MED13, Cyclin C, and Cyclin-dependent kinase 8 (CDK8). In uterine leiomyomas, *MED12* has a very specific mutation pattern, with potential gain-of-function in-frame missense and splice site mutations clustering in exon 2 hot spots. Importantly, although the *MED12* mutations identified were heterozygous, the authors demonstrated that the mutations were nearly always present in the expressed copy of the X chromosome, suggesting that aberrant MED12 function is selected for during tumorigenesis. Given the known role of the Mediator complex, MED12 may be involved in the transcriptional regulation of cancer-related pathways. Indeed, MED12 has been linked to Hedgehog signaling through its interaction with glioma-associated oncogene family zinc finger 3 (GLI3), and WNT signaling through a direct interaction with β-catenin and regulation of WNT target gene expression. Consistent with these previous findings, gene expression analysis of *MED12*-mutant leiomyomas indicated alterations in three major signaling pathways: focal adhesion, extracellular matrix receptor interaction, and WNT signaling. MED12 is now the second component of the Mediator complex that has been implicated in cancer, as *CDK8* amplification has been identified in approximately 50% of colorectal cancers. Interestingly, CDK8 overexpression in colon cancer has also been linked to enhanced β-catenin/WNT signaling, suggesting that deregulation of the WNT pathway may be a common theme among the alterations observed in the kinase module of the Mediator complex.

*Mäkinen N, Mehine M, Tolvanen J, Kaasinen E, Li Y, Lehtonen HJ, et al.* MED12, *the* mediator complex subunit 12 gene, *is mutated at high frequency in uterine leiomyomas. Science. 2011;334:252–55.*

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CANCER DISCOVERY

# *MED12* Mutations are Present in The Majority of Uterine Leiomyomas

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