KMT2D Gene

Subjects: Genetics & Heredity
Contributor: Dean Liu

Lysine methyltransferase 2D

genes

1. Introduction

The *KMT2D* gene, also known as *MLL2*, provides instructions for making an enzyme called lysine-specific methyltransferase 2D that is found in many organs and tissues of the body. Lysine-specific methyltransferase 2D functions as a histone methyltransferase. Histone methyltransferases are enzymes that modify proteins called histones. Histones are structural proteins that attach (bind) to DNA and give chromosomes their shape. By adding a molecule called a methyl group to histones (a process called methylation), histone methyltransferases control (regulate) the activity of certain genes. Lysine-specific methyltransferase 2D appears to activate certain genes that are important for development.

Lysine-specific methyltransferase 2D is also believed to act as a tumor suppressor, which means it normally helps prevent cells from growing and dividing in an uncontrolled way.

2. Health Conditions Related to Genetic Changes

2.1. Kabuki Syndrome

Hundreds of mutations in the *KMT2D* gene have been identified in people with Kabuki syndrome, a disorder characterized by distinctive facial features, intellectual disability, and abnormalities affecting other parts of the body.

The *KMT2D* gene mutations associated with Kabuki syndrome change one building block (amino acid) in the lysine-specific methyltransferase 2D enzyme, delete genetic material in the *KMT2D* gene sequence, or result in a premature stop signal that leads to an abnormally short enzyme. As a result of these mutations, the enzyme is nonfunctional. A lack of functional lysine-specific methyltransferase 2D enzyme disrupts its role in histone methylation and impairs proper activation of certain genes in many of the body's organs and tissues, resulting in the abnormalities of development and function characteristic of Kabuki syndrome.

Although lysine-specific methyltransferase 2D is believed to be a tumor suppressor, a loss of this enzyme's function does not seem to increase cancer risk in people with Kabuki syndrome.

2.2. Cancers

Some gene mutations occur during a person's lifetime. Such mutations, which are called somatic mutations, are present only in certain cells. Somatic mutations in the *KMT2D* gene have been identified in certain cancers. These include medulloblastomas, which are cancerous brain tumors that occur in childhood, and blood-related cancers called lymphomas. Most of these mutations result in an abnormally short, nonfunctional lysine-specific methyltransferase 2D enzyme that cannot perform its role as a tumor suppressor, resulting in the development of cancer.

Increased amounts of lysine-specific methyltransferase 2D and altered distribution of the enzyme within cells have been identified in cancerous tumors of the breast and colon. It is unknown whether these changes result primarily from increased activity (overexpression) of the *KMT2D* gene, extra copies of the gene in tumor cells, altered stability or processing of the enzyme, or other mechanisms. Excess amounts of lysine-specific methyltransferase 2D may disrupt the regulation of other genes. As a result, cells may grow and divide too quickly or in an uncontrolled way, leading to cancer.

3. Other Names for This Gene

- AAD10
- ALL1-related protein
- ALR
- CAGL114
- histone-lysine N-methyltransferase MLL2
- KMT2B
- lysine (K)-specific methyltransferase 2D
- lysine N-methyltransferase 2B
- MLL2
- MLL2_HUMAN
- MLL4
- myeloid/lymphoid or mixed-lineage leukemia 2

- TNRC21
- trinucleotide repeat containing 21

References

1. Bögershausen N, Wollnik B. Unmasking Kabuki syndrome. Clin Genet. 2013Mar;83(3):201-11. doi: 10.1111/cge.12051.
2. Dentici ML, Di Pede A, Lepri FR, Gnazzo M, Lombardi MH, Auriti C, Petrocchi S,Pisaneschi E, Bellacchio E, Capolino R, Braguglia A, Angioni A, Dotta A, Digilio MC, Dallapiccola B. Kabuki syndrome: clinical and molecular diagnosis in thefirst year of life. Arch Dis Child. 2015 Feb;100(2):158-64. doi:10.1136/archdischild-2013-305858.
3. Liu S, Hong X, Shen C, Shi Q, Wang J, Xiong F, Qiu Z. Kabuki syndrome: aChinese case series and systematic review of the spectrum of mutations. BMC MedGenet. 2015 Apr 21;16:26. doi: 10.1186/s12881-015-0171-4. Review.
4. Micale L, Augello B, Maffeo C, Selicorni A, Zucchetti F, Fusco C, De Nittis P,Pellico MT, Mandriani B, Fischetto R, Boccone L, Silengo M, Biamino E, Perria C, Sotgiu S, Serra G, Lapi E, Neri M, Ferlini A, Cavaliere ML, Chiurazzi P, MonicaMD, Scarano G, Faravelli F, Ferrari P, Mazzanti L, Pilotta A, Patricelli MG,Bedeschi MF, Benedicenti F, Prontera P, Toschi B, Salviati L, Melis D, DiBattista E, Vancini A, Garavelli L, Zelante L, Merla G. Molecular analysis,pathogenic mechanisms, and readthrough therapy on a large cohort of Kabukisyndrome patients. Hum Mutat. 2014 Jul;35(7):841-50. doi: 10.1002/humu.22547.
5. Natarajan TG, Kallakury BV, Sheehan CE, Bartlett MB, Ganesan N, Preet A, Ross JS, FitzGerald KT. Epigenetic regulator MLL2 shows altered expression in cancercell lines and tumors from human breast and colon. Cancer Cell Int. 2010 Apr30;10:13. doi: 10.1186/1475-2867-10-13.
6. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI,Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura K, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ, Shendure J.Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. NatGenet. 2010 Sep;42(9):790-3. doi: 10.1038/ng.646.
7. Parsons DW, Li M, Zhang X, Jones S, Leary RJ, Lin JC, Boca SM, Carter H,Samayoa J, Bettegowda C, Gallia GL, Jallo GI, Binder ZA, Nikolsky Y, Hartigan J, Smith DR, Gerhard DS, Fults DW, VandenBerg S, Berger MS, Marie SK, Shinjo SM,Clara C, Phillips PC, Minturn JE, Biegel JA, Judkins AR, Resnick AC, Storm PB,Curran T, He Y, Rasheed BA, Friedman HS, Keir ST, McLendon R, Northcott PA,Taylor MD, Burger PC, Riggins GJ, Karchin R, Parmigiani G, Bigner DD, Yan H,Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The genetic

landscape ofthe childhood cancer medulloblastoma. Science. 2011 Jan 28;331(6016):435-9. doi: 10.1126/science.1198056.

8. Paulussen AD, Stegmann AP, Blok MJ, Tserpelis D, Posma-Velter C, Detisch Y,Smeets EE, Wagemans A, Schrander JJ, van den Boogaard MJ, van der Smagt J, vanHaeringen A, Stolte-Dijkstra I, Kerstjens-Frederikse WS, Mancini GM, Wessels MW, Hennekam RC, Vreeburg M, Geraedts J, de Ravel T, Fryns JP, Smeets HJ, DevriendtK, Schrander-Stumpel CT. MLL2 mutation spectrum in 45 patients with Kabukisyndrome. Hum Mutat. 2011 Feb;32(2):E2018-25. doi: 10.1002/humu.21416.