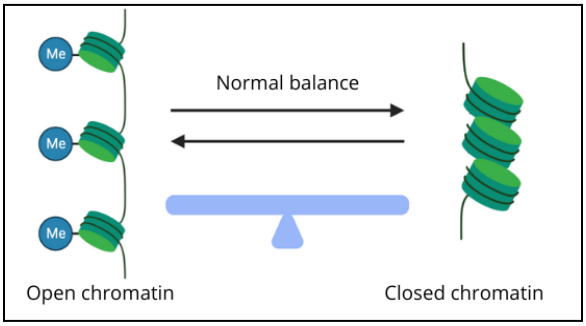
Understanding the Epigenetic Mechanisms of Kabuki Syndrome

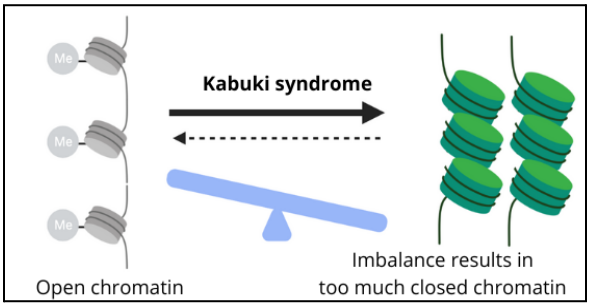
To date, researchers have identified two genes that can cause Kabuki syndrome when variants in the gene code or spelling result in dysfunction of the protein - known as pathogenic variants. Pathogenic variants in the *KMT2D* gene (formerly known as *MLL2*) account for 75% of cases.[1] Pathogenic variants in the *KDM6A* gene account for ~10% of cases.[1] Pathogenic changes in these genes can cause epigenetic changes. Understanding these changes may be key to identifying therapeutic targets and developing treatments.[2]

DNA is the language of life, and how the cells in our bodies know what to do. The entirety of our DNA is the human genome, or "book of life." If the genome is a book, the genes are the words. Even though researchers have had the entire human genome "book" for over 20 years, they are still learning how to read it. Each gene ("word") can have hundreds of different meanings. One way to read a book in different ways is to highlight the words that you need, and maybe you even have a different color highlighter for different types of words. Your genome's highlighting system, or how your DNA is read, is your epigenetics.

Epigenetics are reversible and affected by your environment, including diet and drugs. Epigenetic marks (like highlights) change how the DNA is read, but not the DNA itself. Note that your DNA is not floating around in long lines, but it is often tightly packed into **chromatin** - a mixture of DNA wrapped around histone proteins that provide structural support. Epigenetic "highlights" in the form of histone marks can be added (highlighted) or removed (erased), changing which information in the DNA is read. Your genes and epigenetics normally complete these jobs of highlighting and erasing in a balanced way.

KMT2D is one such highlighter or writer. KMT2D marks histones to open chromatin, enables the DNA to be read, and ultimately influences gene expression (how your body looks and functions). **Variants in KMT2D that cause Kabuki syndrome result in too much closed chromatin**, and the instructions in DNA cannot be read. Without these instructions, gene expression is changed during development and throughout life, and this leads to the symptoms of Kabuki syndrome. **Researchers are exploring different ways to restore the balance between open and closed chromatin to treat symptoms of Kabuki syndrome.[2]**





Pathogenic variants in KDM6A also result in too much closed chromatin but in a different way. KDM6A "erases" or removes a close chromatin mark. If the marks to close the chromatin are not appropriately erased, too much chromatin is closed and an imbalance occurs. **Researchers are also exploring ways to restore the balance between open and closed chromatin to treat symptoms in people with a KDM6A mutation.[2]**

Some individuals are clinically diagnosed with Kabuki syndrome. This means that no pathogenic variant was found on either gene, or that genetic testing was not completed or did not include these genes. In the future, additional genes and gene mutations that cause Kabuki syndrome may also be discovered.

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