

# An Unexpected Gene Important in Brain Infection



By Julianna LeMieux — March 2, 2018



Gene [1]

For most children, an infection with a virus like herpes simplex or influenza (the flu) will cause the typical symptoms and run its course.

But, for about one out in every 10,000 people who are exposed to these common viruses, a potentially deadly disease, encephalitis, develops. Encephalitis, inflammation of the brain, is caused by the viruses ability to invade the brainstem. But, why does this happen to a small subset of otherwise healthy children?

The Casanova lab at The Rockefeller University recently published research that provides a potential answer to this question. They studied seven children from unrelated families who had been exposed to a common virus (herpes simplex virus 1, influenza virus, or norovirus) and developed a life-threatening or lethal infection of the brain stem.

In doing so, they identified mutations in a single gene that may explain what goes wrong in cases of encephalitis of the brain stem.

The gene that the patients had mutations in is called DBR1, and was found to be expressed all over the body, but, had the most expression in the spinal cord and brainstem.

## **What is DBR1 and how could a mutation in it cause encephalitis?**

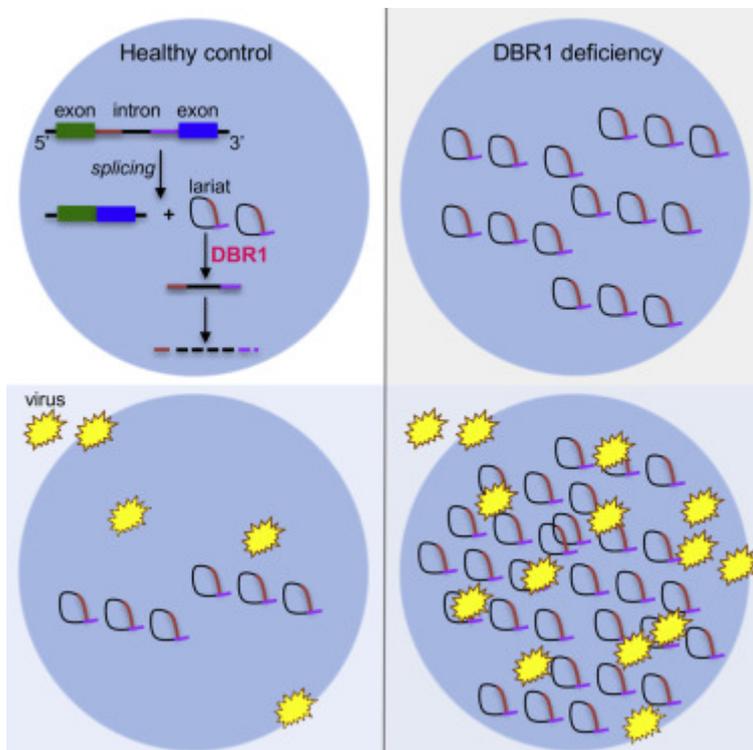
DBR1 encodes the only known RNA lariat debranching enzyme. What is that?

mRNA goes through multiple steps to become the final product that is translated into proteins. These steps are part of the process known as splicing. The mRNA is cut and pasted so that the necessary parts are retained and pasted together and the other parts are discarded. In this process, loops called lariats are formed. This is where DBR1 comes in. The DBR1 protein helps

process these loops. Without it, the lariats remain looped and that can be a problem.

As seen in the figure below, in the panel on the left (healthy control) DBR1 processes the lariats on the mRNA, removing the loops in the RNA, leaving linear RNA pieces. In the panel on the right (DBR1 deficiency), the lariats are unprocessed and the looped RNA remains.

The children in the study who had encephalitis had mutations in both of their copies of the DBR1 gene and, therefore, produced almost none of the DBR1 protein.



The researchers found that fibroblasts of these *DBR1*-mutated patients contain higher RNA lariat levels than control cells. Not only were the patients' fibroblasts highly susceptible to infection with Herpes Simplex virus, but, the lariat levels were increased during this infection as well.

This work is fascinating on multiple levels. First, because a genetic mutation in one gene may be responsible for a very severe clinical outcome. And, that is exciting because since gene mutations may be able to be fixed. But, as a scientist, the link between a basic RNA processing mechanism and immunity in the brain is a leap that is not normally made. Unexpected discoveries like this don't come along every day. But, when they do, they remind us of why basic research is so important and, quite frankly, so incredibly cool.

**Source** [2]: Zhang, Shen-Ying et al. Inborn Errors of RNA Lariat Metabolism in Humans with Brainstem Viral Infection Cell , Volume 172 , Issue 5 , 952 - 965.e18

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[1] <https://pixabay.com/en/dna-biology-medicine-gene-163466/>

[2] [http://www.cell.com/cell/fulltext/S0092-8674\(18\)30163-6](http://www.cell.com/cell/fulltext/S0092-8674(18)30163-6)