Summary of the study *"JNK Inhibitor Suppresses CASK Deficiency-Induced Cerebellar Granular Cell Death in MICPCH Syndrome Model Mice." By Q. Guo, E. Kouyama-Suzuki, Y. Shirai and K. Tabuchi*

Background: Microcephaly with pontine and cerebellar hypoplasia (MICPCH) is a rare and severe brain disorder, mostly seen in girls. It's caused by problems with a gene called *CASK*, which plays a crucial role in brain development. People with this condition have small brains and serious developmental delays. Right now, there's no cure or effective treatment for MICPCH. The CASK gene helps brain cells communicate and survive. When this gene doesn't work properly, certain brain cells—especially those in the cerebellum, which controls movement—begin to die. This study focused on understanding *why* these cells die and how we might be able to stop that from happening.

Discovering the Cell Death Pathway: The researchers used mouse models and brain cell cultures to mimic the effects of CASK deficiency. They discovered that without *CASK*, brain cells activate a harmful chain reaction involving something called the "JNK pathway." This pathway leads to stress and damage inside the cells, mainly through toxic molecules known as "reactive oxygen species" (ROS), which eventually cause the cells to die.

Testing a Potential Treatment: To see if they could interrupt this destructive process, the team tested several drugs known as JNK inhibitors. These drugs are designed to block the JNK pathway. One drug in particular—JNK-IN-8—stood out. When added to the cells in the lab, it reduced the toxic stress and significantly improved cell survival.

From the Lab to Living Mice: The next step was to see if the treatment worked in live animals. The researchers gave JNK-IN-8 directly into the brains of young female mice that had been genetically engineered to have MICPCH (it couldn't be done on male mice since these mice do not survive postnatally). The results were impressive: the treated mice showed fewer signs of brain cell loss, gained weight, and their movement abilities (like walking and limb coordination) improved compared to untreated mice. These behavioural analyses indicate that the cerebellar function is improved by the administration of JNK-IN-8.

Why This Matters: This study is important because it shows that the brain cell death caused by *CASK* deficiency might not be irreversible. By targeting the JNK pathway, the researchers found a way to protect brain cells and improve motor function. This offers real hope for developing treatments for MICPCH—a disorder that currently has very few options.

Limitations and Future Directions: While these results are promising, the study was done in mice, not humans. It's also unclear how long-lasting the effects of the treatment are, or if there might be side effects. More research is needed, including studies on how JNK inhibitors might affect other types of brain cells or interact with other medications.

The Big Picture: Even though MICPCH is rare, understanding it can help scientists learn more about how the brain develops and what happens when key genes go wrong. This study not only sheds light on a rare disease but also opens doors to potential therapies for other neurodevelopmental disorders linked to similar pathways.

Conclusion: By pinpointing how *CASK* gene defects trigger brain cell death and identifying a drug that can block this process, this research offers a new therapeutic direction for a condition that has long been considered untreatable. It's a significant step toward hope for families affected by MICPCH.