

Rett Syndrome Gene Therapy

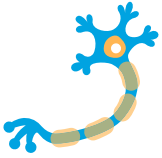
Understanding Taysha's
investigational approach:

TSHA-102



Taysha
GENE THERAPIES

Why genes are important



Our bodies are made up of many types of cells, including brain and nerve cells (neurons). Most neurons, like other cells in the human body, typically contain two copies of each gene carried on DNA (one from each parent).^{1,2}



Genes provide “instructions” to the body’s cells on how to make the proteins needed for a person to develop, grow, and thrive. Each gene makes specific proteins, and these proteins help the body function properly.²



Genetic disorders happen when there is a change (or mutation) in the “instructions” of a gene. Changes like this can result in the body^{3,4}:

- Making a protein that doesn't work correctly
- Making too much of a protein
- Not making enough of a protein
- Not making any of a needed protein

Rett syndrome is caused by a mutation in the *MECP2* gene. These mutations can cause some cells in the body to make either too little working MeCP2 protein or none at all.^{5,6}



The role of the *MECP2* gene

Think of the *MECP2* gene as the stage manager of a play^{7,8}

The stage manager works behind the scenes, **guiding** timing, **coordinating** lighting and sound, and **helping** everyone know when and how to do their role.

When the *MECP2* gene is disrupted, it's like the stage manager went missing.

The people doing different jobs are still on stage, but they no longer have clear direction. The curtains may drop at the wrong time, sound effects might blare or cut out, and actors might miss their cues.



Without the **coordination** of the stage manager, the entire production feels disorganized and doesn't go as planned.

MeCP2 is a protein that helps brain cells work properly by turning important genes on and off. Without it, brain cells don't function as they should, which leads to the symptoms of Rett syndrome.

Did you know?

Although the *MECP2* gene is large and complex, scientists have learned which parts are most important for how it works—helping shape new gene therapy strategies.⁹

Gene therapy for Rett syndrome

A gene therapy for Rett syndrome is designed to treat the root cause of the condition, with the goal of improving symptoms and supporting functional abilities.

It does this by delivering a working copy of the *MECP2* gene to cells in the brain and central nervous system. Once inside, it helps guide cells to make the MeCP2 protein they need.⁹



AAV9 gene therapies

Gene therapies for Rett syndrome use a delivery system based on a virus called AAV9.^{9,10}

To create the gene therapy, the DNA from the virus is removed and replaced with a working copy of the *MECP2* gene.^{10,11}

An AAV9-based gene therapy is designed to be a one-time treatment. A gene therapy for another disease using AAV9 has been shown to be safe and to continue working over time in thousands of patients, both in clinical studies and everyday medical practice.^{10,12-14}

About TSHA-102

TSHA-102 was carefully designed with a version of the *MECP2* gene that is well suited for delivery using AAV9. **TSHA-102** includes the essential parts of the *MECP2* gene required to make functional MeCP2 protein.^{9,15}

This streamlined approach helps the therapy fit within the delivery system and allows room for added features to support how the therapy works in the body and how it is administered, including^{9,15}:

- ✓ **Double-stranded DNA**
- ✓ **A regulatory element (miRARE)**
- ✓ **Intrathecal (IT) delivery**

DOUBLE-STRANDED DNA

Genes are made up of two DNA strands that work together like a zipper to make proteins²

TSHA-102 gene therapy^{9,15-18}



TSHA-102 delivers a **double strand of DNA** to cells, which is like providing both sides of the zipper.

These strands “zip” together immediately upon entering the cell, helping the gene therapy make MeCP2 protein more quickly and reliably—about 10 to 100 times better than single-stranded approaches.

Single-strand therapy^{9,17-19}



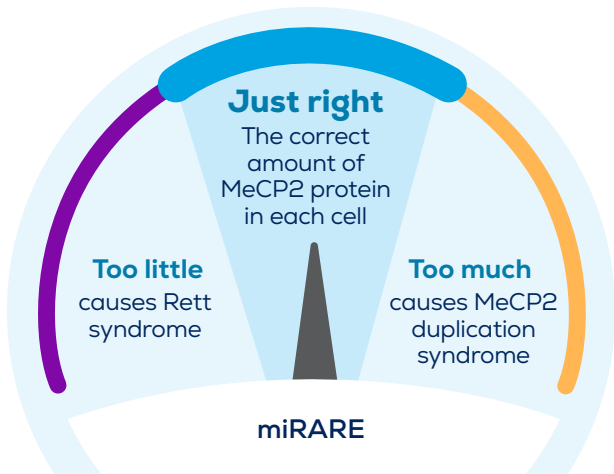
Some gene therapies only deliver **one strand of DNA**, which is like providing one side of a zipper.

This means the cell has to make the other side before it can start, which takes time and can lead to errors.

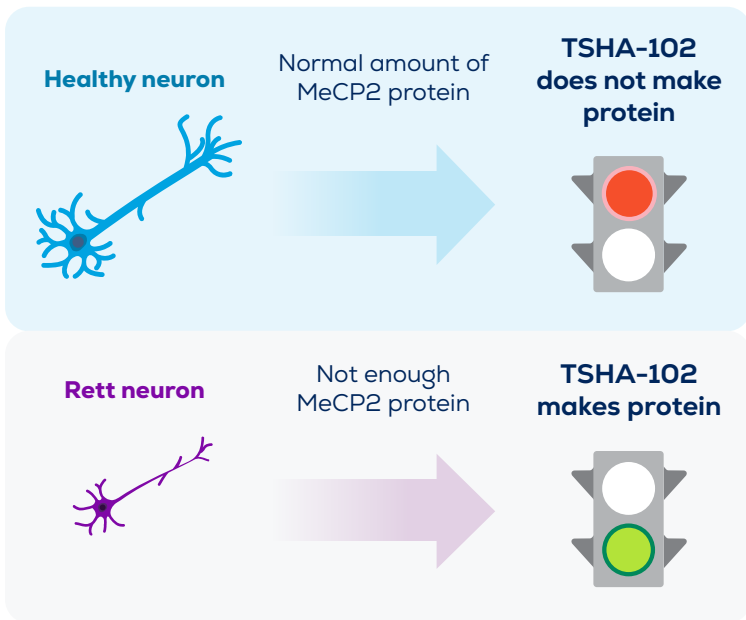
VS

miRARE

Healthy brain function depends on the precise amount of MeCP2 protein. **TSHA-102**'s built-in control sensor—**miRARE**—helps to ensure that each cell gets the right amount of protein, not too much and not too little.^{15,16,20,21}



Using **miRARE** technology, **TSHA-102** has the ability to turn itself on or off depending on the amount of MeCP2 protein in each cell.^{15,16}



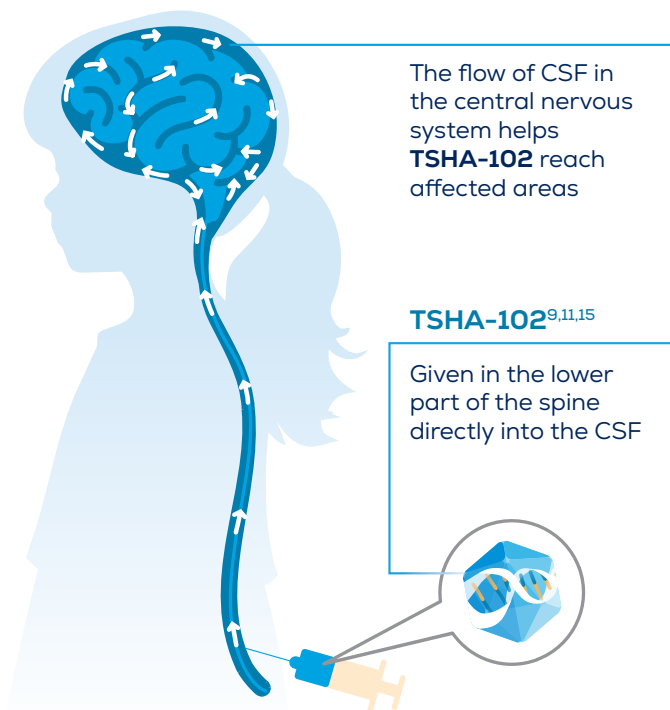
TSHA-102 targets the areas impacted by Rett^{9,16}

TSHA-102 is given through an **intrathecal (IT) injection** in the lower back, also known as a **lumbar puncture (LP)**. This delivers the therapy directly into the fluid that circulates around the brain and spinal cord—called **cerebrospinal fluid (CSF)**. IT delivery has been shown to provide broad and consistent distribution across the central nervous system.^{9,11,15}

This allows the therapy to target the areas of the brain affected by Rett syndrome, including those involved in **movement, communication, social interaction, body functions, and seizures**.^{9,16}

IT DELIVERY

A common, **minimally invasive** way to deliver treatment into the central nervous system, potentially limiting side effects on other organs^{9,16,22,23}



Want to learn more about gene therapy?

Explore helpful resources from the American Society of Gene and Cell Therapy at patienteducation.asgct.org

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