

Understanding TSHA-102

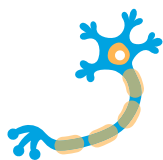


A Caregiver's Guide to an
Investigational Gene Therapy
for Rett Syndrome



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 mutations in the *MECP2* gene, resulting in too little or no functional MeCP2 protein. Without enough MeCP2 protein, brain and nerve cells cannot work properly, leading to the symptoms of Rett syndrome.^{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

Gene therapy for Rett syndrome is designed to address the underlying cause of the condition by providing cells with a functional copy of the *MECP2* gene, with the goal of supporting meaningful gains in function and improving symptoms.

Although brain and nerve cells remain intact, they cannot work properly without enough functional MeCP2 protein. Gene therapy delivers a functional copy of the *MECP2* gene to these cells, providing instructions to make MeCP2 protein that may help them regain function.^{6,9}



AAV9: a delivery vehicle for gene therapy

Gene therapies for Rett syndrome use a well-studied, modified virus called AAV9 to deliver a functional *MECP2* gene to cells in the nervous system.^{9,10}

To create the therapy, AAV9's viral genetic material is removed and replaced with a functional *MECP2* gene. The modified AAV9 carries the gene into cells, where it provides instructions for making functional MeCP2 protein.^{10,11}

An AAV9-based gene therapy is designed to be a one-time treatment. Experience with an AAV9-based gene therapy for another disease has 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^{9,15-17}



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}



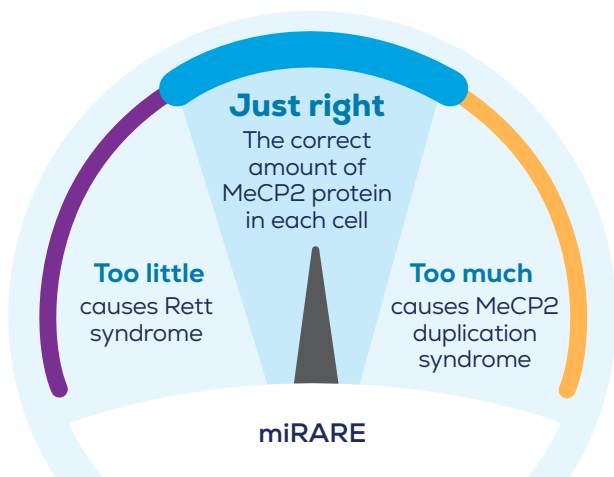
Some gene therapies only deliver **one strand of DNA**, which is like providing one side of a zipper.

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

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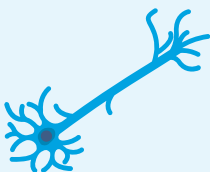
miRARE

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^{15,16,18-20}



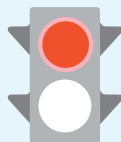
Using **miRARE** technology, **TSHA-102** has the ability to turn itself on or off depending on the amount of MeCP2 protein in each cell.^{15,16}

Healthy neuron



Normal amount of MeCP2 protein

TSHA-102 does not make protein



Rett neuron



Not enough MeCP2 protein

TSHA-102 makes protein



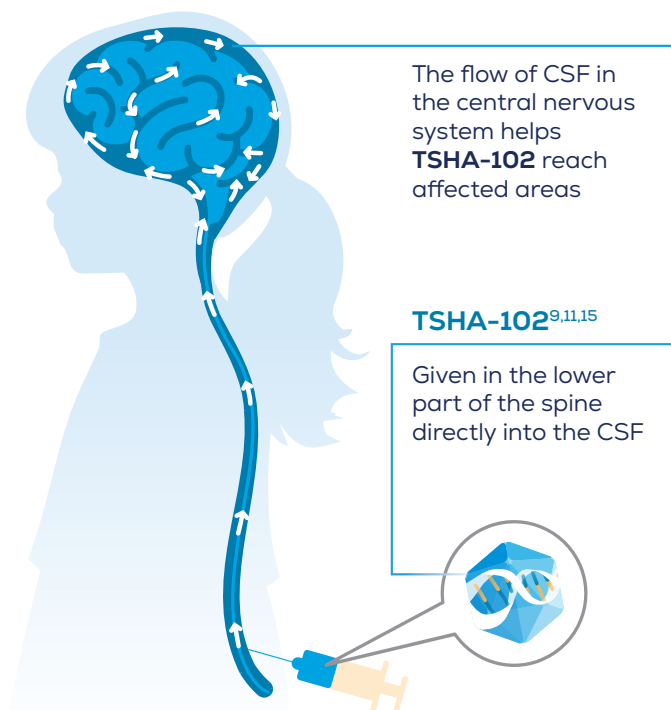
TSHA-102 targets the areas impacted by Rett^{9,16}

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^{9,16,21,22}



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