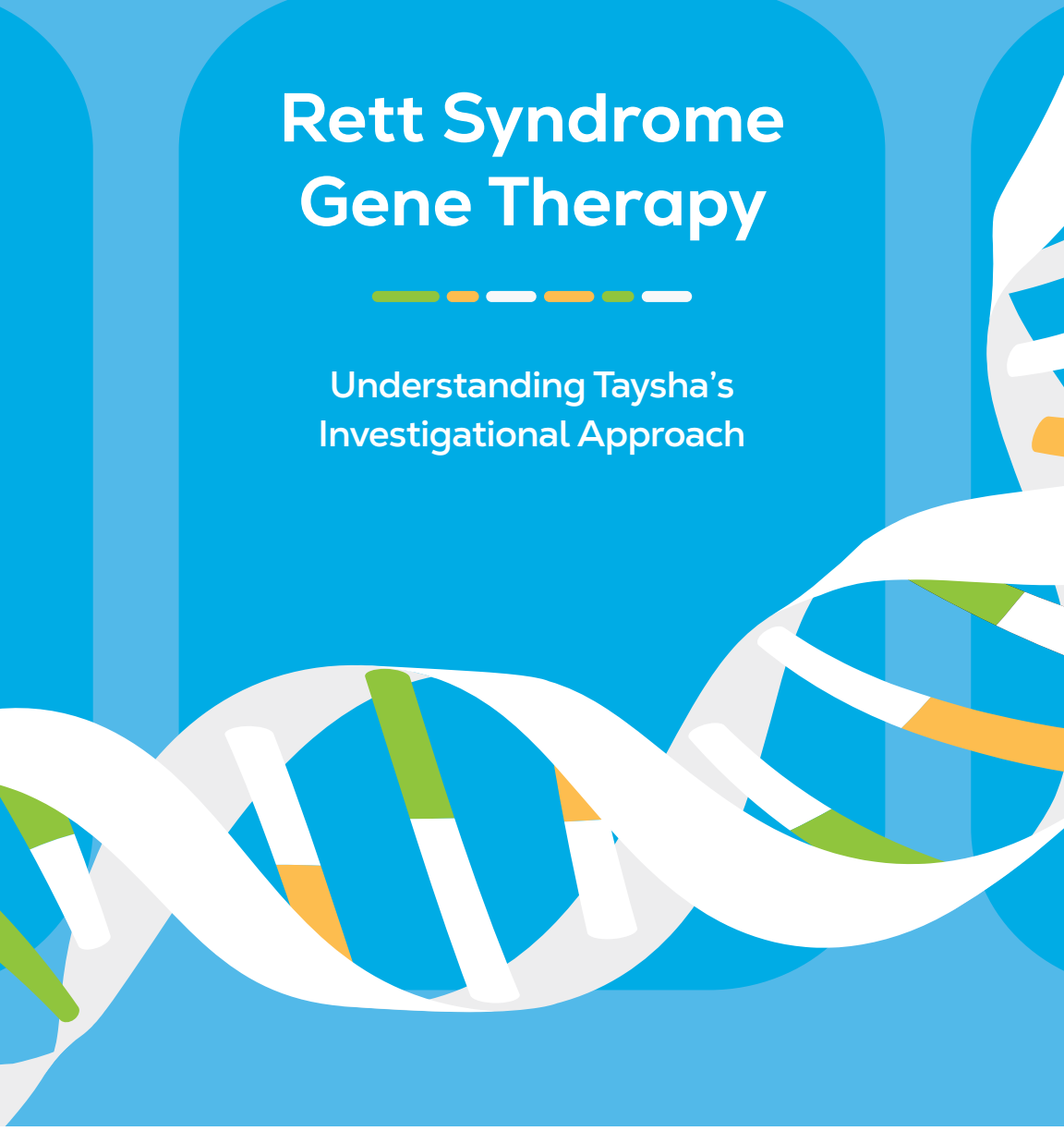
Rett Syndrome Gene Therapy

Understanding Taysha's Investigational Approach



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Understanding Genetic Disorders

Our bodies are made up of many types of cells, including brain and nerve cells.[1] Most brain and nerve cells, like other cells in the human body, typically contain two copies of each gene.[1]

Genes provide "instructions" for how the body can make the proteins needed for a person to grow, develop, and survive. Each gene makes proteins that have specific roles in the body.[1] Proteins are necessary for the body to function properly.[1]

Genetic disorders happen when a mutation, or change in the "instructions," within a gene or multiple genes, occurs.[2] These changes can result in the body:

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

Rett syndrome is considered a monogenic disease, which is because it is primarily caused by mutations in one gene - the *MECP2* gene.[2]

The Underlying Cause of Rett Syndrome

In patients with Rett syndrome, the body doesn't produce, or produce enough, MeCP2 protein.[3,4]

This shortage, caused by a mutation in the *MECP2* gene, changes the activity of the other genes usually controlled by the MeCP2 protein. A lack of MeCP2 protein disrupts brain and nerve development, as well as function and overall health of the nervous system.[3,4]

Gene Therapy for Rett Syndrome

Rett syndrome gene therapy is designed to affect the root cause of the disease by delivering a healthy copy of the *MECP2* gene to cells throughout the brain and central nervous system.[5] Once there, the healthy copy of the gene can provide instructions on how to make MeCP2 protein.[5]

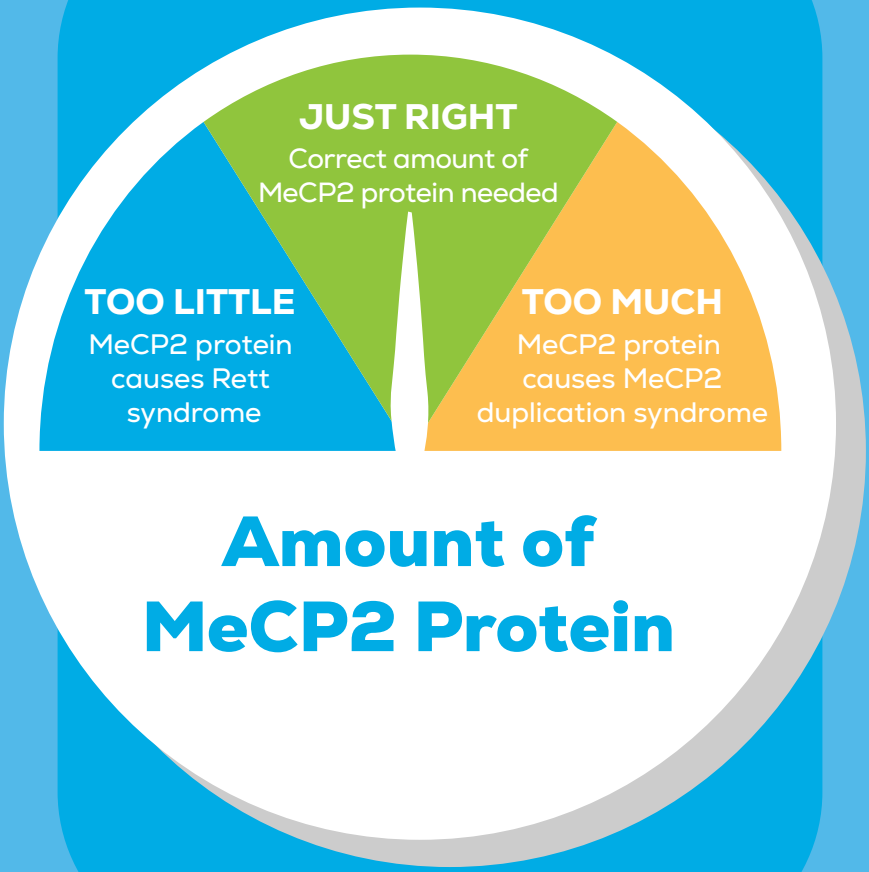
Gene therapies are designed to be a one-time treatment.[6] The healthy gene is placed in a harmless virus (AAV capsid), which acts as a delivery vehicle to bring the gene to target cells.[6]

MeCP2 Protein Levels Need to be Just Right

Most individuals with Rett syndrome have two *MECP2* genes in each cell, but one is randomly turned off (inactivated). This means some cells have a working *MECP2* gene, while others have the non-working version, leading to a mixture of healthy cells and cells affected by the mutation throughout the body.[4]

Brain and nerve cells are highly sensitive to MeCP2 protein. It is crucial for each cell to have the right amount of MeCP2 protein—neither too much nor too little—for proper brain and nervous system function.[7]

Gene therapy for Rett syndrome needs to carefully control the amount of MeCP2 protein in each cell. The goal is to make the right amount of MeCP2 protein to restore function in the cells that need it, without causing harm from excess MeCP2 protein in the cells that don't need it.[7]



Amount of MeCP2 Protein

Taysha's Investigational Gene Therapy Approach (TSHA-102)

Taysha's investigational gene therapy approach for Rett syndrome is made up of a **mini*MECP2* gene, miRARE**, and **self-complementary vector**:[5]

mini*MECP2* gene

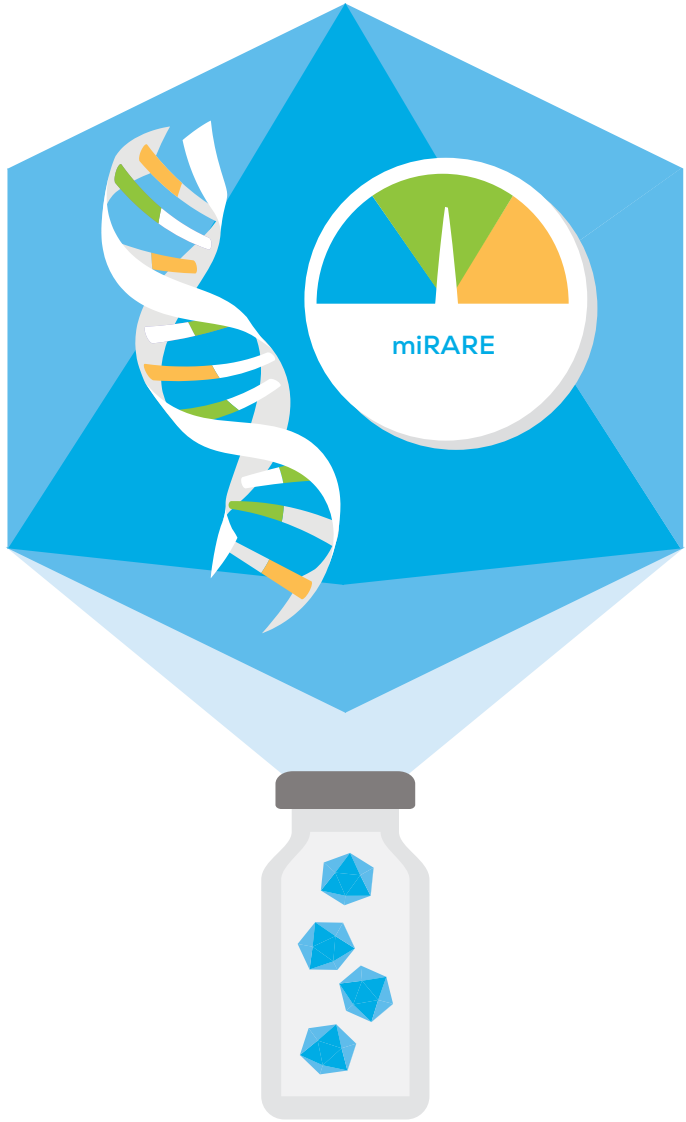
The mini*MECP2* gene used in TSHA-102 contains the essential parts of the *MECP2* gene responsible for producing a functional MeCP2 protein.[5,8] The smaller size offers benefits too– the minigene can be packaged with miRARE and a self-complementary vector.

miRARE

Once TSHA-102 reaches the target cell, miRARE determines whether the levels of MeCP2 protein in the cell are sufficient. It then works to "turn on" or "turn off" MeCP2 protein production, so that it is only made in the cells that need it. miRARE does this on a cell-by-cell basis, ensuring MeCP2 protein levels in each cell are just right – not too much or too little.[7]

SELF-COMPLEMENTARY VECTOR (scAAV)

scAAV is a gene therapy delivery method that is more efficient than single-stranded AAV in providing instructions for cells to produce proteins.[9] Because of this enhanced efficiency, scAAVs have been shown to achieve similar or better results at lower doses than single-stranded AAV.[10] Using a lower dose of gene therapy may cause fewer side effects and be better tolerated by the body.



ROUTE OF ADMINISTRATION

TSHA-102 is given through an intrathecal injection in the lumbar region of the spine (spinal tap), a well-known minimally invasive medical procedure that delivers the therapy directly into cerebrospinal fluid (CSF).[10] CSF naturally and consistently flows through the brain and spinal cord, ensuring widespread biodistribution across the brain and spinal cord regions impacted in Rett syndrome.[11,12]

For more information about gene therapy, visit the American Society of Gene and Cell Therapy at patienteducation.asgtc.org.

References: 1. U.S. National Library of Medicine. *What is a gene?: Medlineplus Genetics*. MedlinePlus. https://medlineplus.gov/genetics/understanding/basics/gene **2.** National Human Genome Research Institute. *Genetic Disorders*. https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders **3.** U.S. National Library of Medicine. *Rett syndrome: Medlineplus Genetics*. MedlinePlus. https://medlineplus.gov/genetics/understanding/basics/gene **4.** International Rett Syndrome Foundation. *About Rett Syndrome*. https://www.rettsyndrome.org/about-rett-syndrome/ **5.** Sadhu C, et al. *Genes*. 2024;15:31. **6.** MedlinePlus. Help Me Understand Genetics. Gene Therapy and Other Medical Advances. https://medlineplus.gov/download/genetics/understanding/therapy.pdf **7.** Sinnet SE, et al. *Brain*. 2021;144(10):3005–19. **8.** Tillotson R, et al. *Nature*. 2017; 550(7676):398–401. **9.** McCarty DM. *Mol. Therapy*. 2008;16(10):1648–1656. **10.** Gray SJ, et al. *Gene Therapy*. 2013;20(4):450–459. **11.** Perera A, et al. *Acta Neurochir* (Wien). 2024;166(1):136. **12.** Özütemiz C, et al. *Diagn Interv Radiol*. 2020;26(6):596–602.

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TSHA-102_Gtx Broch_USA_English_V2.0_15APR2025
TSHA-RET-375-2024