



## National Tay-Sachs & Allied Diseases Association

### **What is gene therapy?**

Our genes provide specific instructions to make proteins, which carry out essential functions in our bodies. If a gene has a harmful change (i.e., pathogenic variant), it may not provide correct instructions to produce functional proteins. Some genetic mutations are linked to the development of specific conditions. Tay-Sachs, Sandhoff, GM1 gangliosidosis, and Canavan disease are all genetic conditions caused by pathogenic variants in specific genes.

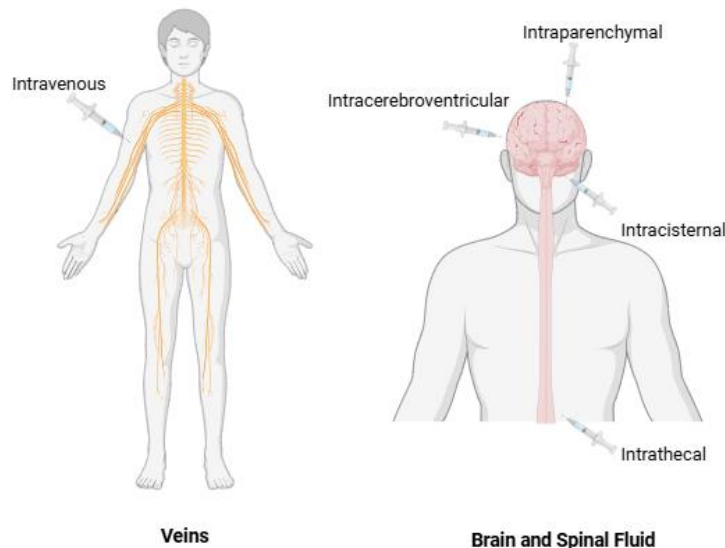
**Gene therapy is a technique that uses genetic material to stop or slow the progression of disease. Typically, this is done by introducing working copies of a defective gene into specific cells in the body.**

### **How is this gene therapy delivered?**

Working copies of the gene are delivered into the cells using a vector. A vector is a delivery vehicle that can get into cells and deliver new genetic material. Adeno-associated virus (AAV) vectors are the most common type of vector used in gene therapy for Tay-Sachs, Sandhoff, GM1 gangliosidosis, and Canavan disease and are proven to be generally safe. The vector's viral genes are replaced by therapeutic genes before delivery into specific cells.

The routes of AAV vector delivery can vary between studies and can include delivery directly into certain areas of the brain or spinal fluid. The figure below adapted from PMID: 33895085 depicts some of the most common approaches.

### Potential AAV Gene Therapy Delivery Routes for Central Nervous System Diseases



Created in BioRender.com bio

### What are the limitations of AAV gene therapy?

**Immune responses:** Patients may have an immune response against AAV vectors. To minimize this risk, administration is typically limited to one dose and immunosuppressive drugs may be given during treatment (PMID: 35994385).

**Delivery:** Direct injections into the brain and spinal fluid may be used, and these are very invasive procedures.

**Age:** Gene therapies are most effective when given at younger ages, as early treatment can minimize damage caused by the condition (PMID: 30524313; PMID: 30524313).

**Accessibility:** Currently, there are no FDA approved therapies, although clinical trials are ongoing for the four diseases NTSAD represents. Gene therapy in general remains expensive and inaccessible to many.

**Outcomes of trials:** While clinical trials are ongoing, more research is needed to understand the efficacy and safety of these gene therapies in patients. Patients participating in clinical trials should be informed of any benefits and risks of participation.

**Unknown long-term effects:** Because gene therapy clinical trials in patients have only recently begun, the long-term effects, both good and bad, are not well understood.

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## **Gene therapy for GM2 gangliosidoses (Tay-Sachs and Sandhoff diseases)**

The *HEXA* and *HEXB* genes provide the body with instructions to make an enzyme called beta-hexosaminidase A (HexA). This enzyme helps break down fatty substances in the body's brain and nerve cells.

When there is a defective *HEXA* or *HEXB* gene due to a genetic change, HexA cannot do its job properly. As a result, there is a toxic buildup of fatty substances, which damages the brain and spinal cord.

### **Gene therapy aims to stop or slow the progression of GM2 gangliosidoses by introducing working copies of the *HEXA* and *HEXB* genes into brain and nerve cells.**

AAV gene therapy for GM2 gangliosidoses is typically administered through injections into the brain and/or spinal cord. This allows the therapy to directly reach the brain and nerve cells.

Clinical trials are a type of medical research that explores if a specific treatment is safe and effective in human participants. Gene therapy clinical trials for GM2 gangliosidoses are ongoing with the hopes of finding a potential treatment for the disease. The [clinicaltrials.gov](https://clinicaltrials.gov) website is a searchable database listing clinical trials.

### **What gene therapy clinical trials are currently ongoing for GM2 gangliosidoses?**

#### **University of Massachusetts Medical School (Active, not recruiting)**

A Dose-escalation and Safety & Efficacy Study of AXO-AAV-GM2 in Tay-Sachs or Sandhoff Disease: [Clinical Trial #NCT04669535](#)

This clinical trial involves a bilateral intraparenchymal thalamic and intracisternal/intrathecal administration of AXO-AAV-GM2 (AAVrh8-HEXA and AAVrh8-HEXB) gene therapy in patients with infantile or juvenile onset (6 months to 12 years old) Tay-Sachs or Sandhoff disease.

#### **Queen's University (Not Active)**

First-in-Human Study of Gene Therapy for Treatment of Infantile Onset GM2 Gangliosidosis: [Clinical Trial #NCT04798235](#)

This clinical trial involves intrathecal administration of TSHA-101 (AAV9) gene therapy in patients with infantile onset (up to 15 months old) GM2 gangliosidosis.

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For more detailed information about gene therapy for GM2 gangliosidoses, please see our document: [Gene Therapy – GM2 Gangliosidoses](#)

For more information of gene therapy for GM2 gangliosidoses, please check out this educational resource created by ASGCT (American Society of Gene and Cell Therapy): <https://patienteducation.asgct.org/disease-treatments/gm2-tay-sachs-sandhoff>

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### **Gene therapy for Canavan disease**

The *ASPA* gene provides the body with instructions for how to make an enzyme called aspartoacylase (ASPA). This enzyme plays an important role in the proper formation of myelin, a fatty substance that protects nerves in the brain.

When the *ASPA* gene does not work properly, nerve cells are unprotected and cannot send and receive messages properly, which damages the brain and spinal cord.

**Gene therapy aims to stop or slow the progression of Canavan disease by introducing working copies of the *ASPA* gene into brain and nerve cells.**

AAV gene therapy is administered through injections into the veins (intravenously) or into the brain or spinal fluid.

Clinical trials are a type of medical research that explores if a specific treatment is safe and effective in human participants. Gene therapy clinical trials for Canavan Disease are ongoing with the hopes of finding a potential treatment for the disease.

### **What gene therapy clinical trials are currently ongoing for Canavan disease?**

#### **Aspa Therapeutics (Recruiting)**

A Study of AAV9 Gene Therapy in Participants With Canavan Disease: [Clinical Trial #NCT04998396](#)

This clinical trial involves intravenous administration of AAV9 BBP-812 (AAV9) gene therapy in pediatric patients (up to 30 months old) with Canavan disease.

#### **Myrtelle LLC, Gene Therapy (Recruiting)**

rAAV-Olig001-ASPA Gene Therapy for Treatment of Children With Typical Canavan Disease (CAN-GT): [Clinical Trial #NCT04833907](#)

This clinical trial involves a single dose intracerebroventricular administration of rAAV-Olig001-ASPA gene therapy in patients (3 months to 60 months old) with Canavan disease.

For more detailed information about gene therapy for Canavan disease, please see our document: [Gene Therapy – Canavan Disease](#)

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## **Gene therapy for GM1 gangliosidosis**

The *GLB1* gene provides the body with instructions for how to make an enzyme called beta-galactosidase. These enzymes play important roles in breaking down fatty substances in the body's brain and nerve cells.

When the *GLB1* gene does not work properly, there is a toxic buildup of fatty substances, which predominantly damages the brain and spinal cord.

**The goal of gene therapy is to stop or slow the progression of GM1 gangliosidosis disease by introducing working copies of the *GLB1* gene into brain and nerve cells.**

AAV gene therapy is administered through injections into the veins (intravenously) or fluid-filled spaces in the brain (intracisterna magna).

Clinical trials are a type of medical research that explores if a specific treatment is safe and effective in human participants. Gene therapy clinical trials for GM1 gangliosidosis are ongoing with the hopes of finding a potential treatment for the disease.

## **What gene therapy clinical trials are currently ongoing for GM1 gangliosidosis?**

### **NHGRI – NIH (Recruiting)**

A Phase 1/ 2 Study of Intravenous Gene Transfer With an AAV9 Vector Expressing Human Beta-galactosidase in Type I and Type II GM1 Gangliosidosis: [Clinical Trial #NCT03952637](#)

This clinical trial involves intravenous administration of AAV9-GLB1 gene therapy in patients with Type I and Type II GM1 gangliosidosis (6 months to 12 years old).

### **Passage Bio (Enrollment paused)**

Study of Safety, Tolerability and Efficacy of PBGM01 in Pediatric Subjects With GM1 Gangliosidosis (Imagine-1): [Clinical Trial #NCT04713475](#)

This clinical trial involves intracisterna magna administration of PBGM01 (AAVhu68) gene therapy in patients with late onset infantile GM1 Gangliosidosis (Type 2a) and early onset infantile GM1 Gangliosidosis (Type 1) (1 month to 24 months old).

For more detailed information about gene therapy for GM1 gangliosidosis, please see our document: [Gene Therapy – GM1 Gangliosidosis](#)

For more information of gene therapy for GM1 gangliosidosis, please check out this educational resource created by ASGCT: <https://patienteducation.asgct.org/disease-treatments/gm1-gangliosidosis>

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For more information about gene therapy, vectors, and the clinical trial process, please check out the following educational resources created by ASGCT:

Gene therapy basics: <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-basics>

Gene therapy approaches: <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-approaches>

Clinical trial process: <https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process>

Vectors 101: <https://patienteducation.asgct.org/gene-therapy-101/vectors-101>

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To access the literature reference, enter the PMID number into the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) search box or Google “PMID XXXXXXXX”, replacing the “X’s” with the appropriate number.

Data is current as of August 2024.

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