

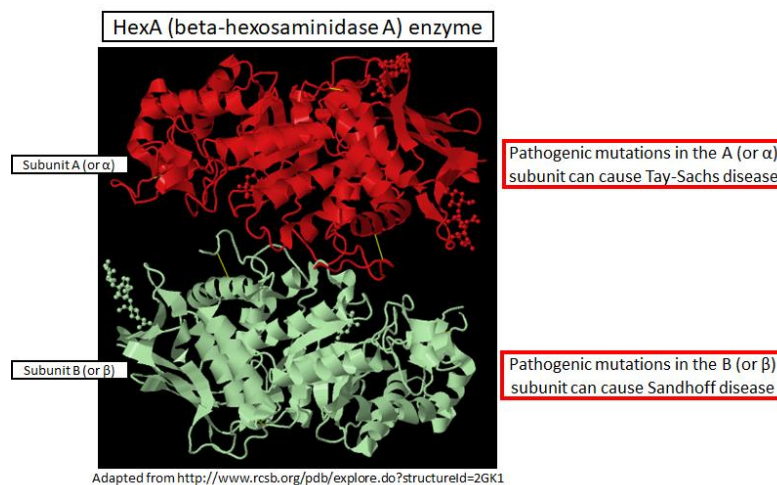


National Tay-Sachs & Allied Diseases Association

Gene Therapy - GM2 Gangliosidosis

Introduction

GM2 gangliosidosis, including Tay-Sachs and Sandhoff diseases, are caused by deficiencies in the enzyme beta-hexosaminidase A (HexA). This enzyme is made up of two different subunits (heterodimeric) and it is responsible for breaking down GM2, a fatty substance found in brain and nerve cells. Tay-Sachs disease is caused by pathogenic variants in the *HEXA* gene that encodes the enzyme's alpha subunit, while Sandhoff disease is caused by pathogenic variants in the *HEXB* gene that encodes the enzyme's beta subunit (see figure below). Pathogenic variants in either subunit cause the HexA enzyme to not work properly. As a result, there is a toxic accumulation of GM2 in the central nervous system (CNS) that leads to progressive neuron loss and degeneration.



Currently, there are no curative therapies for Tay-Sachs or Sandhoff disease. Gene therapy offers promise as it aims to stop or slow the progression of these diseases by introducing working copies of the *HEXA* and *HEXB* genes into brain and nerve cells. The goal is to restore enzyme function and thus reduce GM2 accumulation.

Delivery & Administration

The preferred delivery method for GM2 gangliosidosis gene therapy is currently adeno-associated viral (AAV) vectors.

Previous studies explored alternative delivery methods (i.e. adenoviruses, HSV-1, cross-correction retroviruses), but they were met with significant limitations (PMID: 30524313). These included significant immune responses, insufficient modification of disease traits, and unequal distribution of the therapy in the CNS. AAV gene therapy emerged as a favorable approach to treat GM2 gangliosidosis due to its comparatively lower immunogenicity and its ability to establish long-term, stable gene expression in brain and nerve cells.

Another limitation to other delivery methods was the ability to cross the blood-brain barrier (BBB), which depends on the vector used. The BBB protects the CNS by strictly regulating the transport of substances and drugs, prompting exploration of methods to bypass the BBB to deliver gene therapy to the brain and nerve cells. Some types of AAV vectors may be able to cross the BBB and be delivered intravenously, and research is ongoing to better understand their efficacy. Another method that can bypass the blood-brain barrier is direct injections into the brain and spinal fluid (i.e. intracranial, intrathecal, intracisternal, intraparenchymal, intracerebroventricular). A limitation of this method, however, is that it is a very invasive procedure.

Animal models have shown that AAV vectors allow the HexA enzyme to be expressed throughout the nervous system without notable toxicity to cells (PMID: 30524313). AAV gene therapies have been successful in reducing the amount of GM2 and thus improving symptoms in affected mice and cats, but these results did not apply to non-human primates (PMID: 35865957). A 2021 study involving two infants affected with Tay-Sachs disease demonstrated the feasibility, general safety, and signs of disease stabilization associated with AAV gene therapy (AAVrh8-HEXA and AAVrh8-HEXB) via intracranial thalamic injection (PMID: 35145305).

A functional HexA enzyme, including both alpha and beta subunits encoded by *HEXA* and *HEXB* genes respectively, must be present in the vector to create a clinically significant gene therapy. This is beneficial when creating GM2 gene therapies because one method could theoretically be used to treat both Tay-Sachs and Sandhoff disease. However, some AAV vectors are limited in their DNA carrying capacity, making it challenging to include both *HEXA* and *HEXB* genes into a single (bicistronic) vector (PMID: 30524313). The 2021 study mentioned above used two monocistronic vectors, each carrying either *HEXA* or *HEXB*, to circumvent this limitation. However, using a single bicistronic vector may result in better enzyme expression. Therefore, researchers are exploring ways to create bicistronic vectors that deliver both *HEXA* and *HEXB* into the cells.

Additional avenues are also being explored in animal models including the creation of a single hybrid beta-hexosaminidase subunit (*HEXM*) that forms a stable structure that

includes both alpha and beta subunits into one construct (PMID: 31896760). Animal models using *HEXM* constructs have shown success in restoring motor function and increasing lifespan. However, there remains concern about the functionality and safety of using this in patients, particularly related to concerns about immunogenicity due to the construction of a foreign protein product.

Although AAV vectors exhibit lower immunogenicity compared to other methods, AAV gene therapy has been seen to elicit innate and adaptive immune responses and immune-mediated adverse responses have been observed in clinical trials with AAV gene therapy (PMID: 35994385). To minimize this risk, administration is typically limited to one dose and immunosuppressive therapy is needed in the treatment process. Additionally, vector design continues to be optimized to limit the potential for toxicity.

Because defects in neuronal activity begin *in utero* and worsen over time, gene therapy may work best to reduce when given at younger ages (PMID: 30524313). Most studies have focused on treating the infantile and juvenile forms of the conditions during early manifestations of the disease.

There is a third GM2 gangliosidosis disorder named GM2 Activator Protein Deficiency (AB-Variant or ABGM2) that is caused by pathogenic variants in the *GM2A* gene (PMID: 37834060). However, there have been less than 30 patients reported to date. While research is ongoing, no AB Variant gene therapy clinical trials are currently available.

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

For more information about gene therapy, vectors, and the clinical trial process, please check out the following educational resources created by the American Society of Gene and Cell Therapy (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>

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.