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Gene Therapy for Neurological Disorders-A Review

Pravalika[1], Yuvaraj Babu K[*2], Gifrina Jayaraj[3]

[1]Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[2]Department of Anatomy, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[3]Department of Oral Pathology, Saveetha Dental college and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

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Abstract

This review article is based on improving knowledge on gene therapy which treats many neurological disorders. 150 articles were obtained, and 36 articles were filtered. Gene therapy is one of the most important treatments in the future as well as in the present. It has high chances of reducing many disorders in future. Many neurological disorders have been cured, but still many more researches are being done to express the potential of gene therapy to its maximum. Gene therapy improves the motor system in mouse models. Few neurological disorders that can be treated are Alzheimer's disease and Parkinson's disease. This review is an attempt to update recent advances in gene therapy.

*Corresponding Author

Name: Yuvaraj Babu K
Phone:
Email: yuvarajbabu@saveetha.com

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INTRODUCTION

Genetic diseases can be wiped out by gene therapy before they can begin and eliminate suffering for future generations. The devastating effects of the diseases of the nervous system are prevalent in the elders, which is caused by inherited genetic mutations that lead to neurological problems. This therapy for such diseases has been made progress in understanding the underlying disease mechanisms in those involving sensory neurons is also by the improvement of gene vector design, therapeutic gene selection and methods of delivery (Simonato *et al.*, 2013). Adeno associated viral vectors are the treatment of neurological diseases which is a rapidly emerging therapy platform. In preclinical studies, transgenes encoding therapeutic proteins, MicroRNAs, Antibodies which are gene-editing machinery which has been successfully delivered (Deverman *et al.*, 2018).

Severe combined immune deficiency such as Adenosine deaminase deficiency, hereditary blindness, hemophilia, blood diseases, fat metabolism disorders, cancer and more can be cured by gene therapy. The different target cell population of different vectors and both in vivo and ex Vivo approaches help in treating a variety of disorders (Philippidis, 2020). Researchers testing several approaches to gene therapy by replacing mutated gene with a healthy copy of gene, inactivating or knocking down (out) mutated gene and if the healthy gene is not functioning properly, the introduction of a new gene into the body to fight the disease is done (Hayashi *et al.*, 2020).

Background information on experimental details of gene therapy tools for the neurological disorder was provided. Emerging new technologies such as CRISPR/Cas9 genome was introduced to cure neurodegeneration, muscular dystrophy, trauma, chronic pain and more.gene therapy is a promising treatment for Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and more. Brain delivery of a small engineered antibody recognises toxins in the brain if Alzheimer's disease patients which prevent brain damage and memory loss. Gene therapy holds potential in treating incurable neurological diseases. Preclinical animal studies are essential for more effective ways to deliver genes.

Over the past years various research done by our team was on Osteology (Keerthana and Thenmozhi, 2016; Hafeez and Thenmozhi, 2016; Choudhari and Thenmozhi, 2016) Stature estimation (Krishna and Babu, 2016; Kannan and Thenmozhi, 2016; Nandhini, 2018), use and ill effects of electronic gadgets (Thejeswar and Thenmozhi, 2015; Sriram *et al.*, 2015; Subashri and Thenmozhi, 2016), on RNA (Sekar, 2019; Johnson *et al.*, 2020), animal studies (Seppan *et al.*, 2018; Pratha and Thenmozhi, 2016) and in few other fields (Menon and Thenmozhi, 2016; Samuel and Thenmozhi, 2015). There is a lack of much information on the current topic of gene therapy on neurological disorders. Hence the study's main aim is to improve the knowledge of gene therapy to treat neurological disorders.

MATERIALS AND METHODS

This article is obtained from the Pubmed website and Google Scholar, which is a narrative review of primary research literature. Restrictions were placed in the time period between 1997-2020 and abstract of non-English papers, retracted articles were excluded. International articles were researched for the treatment of neurological disorders by gene therapy. More than 150 articles were obtained and 42 articles were filtered according to the abstract title, complete article and then reviewed. Keywords used for the search were: Gene therapy, neurological disorders, vector, Alzheimer's disease, Parkinson's disease, potential. The level of evidence of the reviewed articles was categorized as per the criteria of Centre for Evidence-Based Medicine, Oxford, UK (Bluhm, 2011) and graded as strong, moderate and weak (Table 1).

Currently available Gene Therapy techniques

Current application of gene therapy help address basic neurological problems. Adeno virus-derived vectors are one of the techniques which immunize humans from natural infections (Lowenstein *et al.*, 2003) Recombinant Adeno Associated virus(rAAV) supports Long term transgene expression which is derived from small human parvovirus (Mandel, 2006). Gene replacement therapy is a cell-based therapy for treating transplantation of neural stem and progenitor cells (Goldman and Windrem, 2006). Adeno associated virus, from 1982 is used to find virology and biology of viruses and improvement of AAV is also done (Coura and Nardi, 2007).

Partial problems derived from Gene Therapy strategies

Mesenchymal stem cells are used for myocardial infarction which has migratory properties of MSCs for any brain injury, and tumours (Picinich *et al.*, 2007). Scientific obstacles, vehicles used to deliver normal genes and immune response of vector becomes devastating are few problems (Ali, 1998) neurological disorders treated by the recent development of gene therapy. This therapy approaches such as addition, knockdown and alteration of genes and correction are used. Gene therapy, in combination with stem cell therapy, is useful for future (Kay *et al.*, 1997) Histone deacetylases, HDAC inhibitors provide autoimmunity. Preclinical models have been tested for finding such results (Falkenberg and Johnstone, 2014).

Alzheimer's disease

To prevent AD, proteins in specific brain regions containing degenerating neurons must be achieved in adequate concentrations which will prevent non-targeted regions from getting infected (Tuszynski, 2007). Stem cell therapy and gene replacement therapy are helpful in treating AD. Prolonged protection of central cholinergic system is the cure which has been done experimentally to prove (Mecocci, 2007). Alzheimer's disease leads to dementia, memory loss and more. Alpha-beta aggregation causes AD-HN derived lentiviral vector to heat. AAV is the most frequently used vector to heat AD (Nilsson *et al.*, 2010). Gene modified cells are the promising therapeutic approach for AD-potential clinical application Cholesterol metabolism is connected to AD-AAV gene therapy reduces the amyloid plaque with cholesterol 24 hydroxylase. It was tested in a mouse having amyloid plaque of AD (Hudry *et al.*, 2010) acyltransferase1 (ACAT1) is which knockdowns Gene therapy and amyloid-beta in a mouse model of AD is reduced (Murphy *et al.*, 2013; Pratha and Thenmozhi, 2016).

Parkinson's disease

Early-stage of PD patients is significant of nigrostriatal dopamine innovation which is the efficacy of GDFLs Symptoms of PD caused by nigrostriatal degeneration, innovative gene delivery disease pathology (Coune *et al.*, 2012). PD has many

Table 1: Description and Quality Assessment of included studies

S No	Author Name (Year)	Type of study	Key points	Quality of Study
1	Simonato *et al.* (2013)	research article	improve gene vector design	Moderate
2	Deverman *et al.* (2018)	research article	AAV ,microRNA	strong
3	Philippidis (2020)	review	in Vivo and ex Vivo	strong
4	Hayashi *et al.* (2020)	research article	knocking down mutated gene	moderate
5	Johnson *et al.* (2020)	review	arterial hypertension	moderate
6	Lowenstein *et al.* (2003)	research article	AAV	Strong
7	Goldman and Windrem (2006)	research article	transplantation	Moderate
8	Coura and Nardi (2007)	research article	virology	Strong
9	Picinich *et al.* (2007)	research article	migratory properties	Moderate
10	Ali (1998)	research article	scientific obstacles	strong
11	Kay *et al.* (1997)	research article	gene therapy approaches	Moderate
12	Falkenberg and Johnstone (2014)	research article	preclinical models	Moderate
13	Tuszynski (2007)	review	brain area	Moderate
14	Mecocci (2007)	review	cholinergic system	strong
15	Nilsson *et al.* (2010)	review	memory loss,dementia	Moderate
16	Hudry *et al.* (2010)	research article	cholesterol metabolism	Strong
17	Murphy *et al.* (2013)	research article	amyloid plaque	Moderate
18	Manfredsson *et al.* (2009)	research article	cure to Parkinson's disease	strong
19	Coune *et al.* (2012)	review	symptoms of parkinson	strong
20	Bartus *et al.* (2014)	research article	dopamine	moderate
21	LeWitt *et al.* (2011)	research article	AAV2- GAD	moderate
22	Palfi (2014)	research article	lentiviral vector based	strong
23	Axelsen and Woldbye (2018)	research article	GABA	weak
24	Ji *et al.* (2013)	research article	CHRs	moderate
25	Mugilan *et al.* (2017)	research article	cure cancer	moderate
26	Hodgson *et al.* (2017)	research article	translations	strong
27	Pagenstecher *et al.* (2009)	review	CRISPR	strong
28	Pena *et al.* (2020)	review	Advancement	weak

gene therapy cures, some are successful by design but failure by efficacy. Oral dopaminergic macromolecules control PD's symptoms (Bartus *et al.*, 2014). AAV2-GAD in the subthalamic nucleus with sham surgery in patients is delivered bilaterally and is done for patients with advanced PD (LeWitt *et al.*, 2011). Gene therapy is safe, tolerable and efficient. Local and continuous dopamine production is restored by lentiviral vector-based therapy (Palfi, 2014). GABA-non disease modify treatment whereas neurotrophic factors are disease-modifying treatment (Axelsen and Woldbye, 2018).

Potential of Gene Therapy

Applying ChRs for treatment is a molecular modification, targeting methods with sophisticated electrical devices are also done in gene therapy (Ji *et al.*, 2013). Gene therapy is used for multiple diseases. GT is also a new option for treatment of various cancers (Mugilan *et al.*, 2017). Regulatory path complex helps in translation process which ensures Long term effects that is best to intervene (Hodgson *et al.*, 2017) promising finding from preclinical animal studies to involve deliver of genes to the spinal cord which is an ongoing research treatment for rare diseases, unique challenges and more effective larger genes and multiple small genes are delivered by promoters. They remain active for a long time.

RESULTS AND DISCUSSION

Potential candidates for gene therapy but are minimally responsive to existing treatments. It involves an outlook of a replacement allele r cells or silencing dominant mutant alleles that is pathological. Neurological Disorders such as PD, AD clinical trials using these approaches are likely to be implemented soon.

(AAV) or vector with an excellent safety profile derived from small human parvovirus. Supporting Long term transgene expression in the nervous system and acting as efficient transducers are few qualities of this vector. Therefore, neurological disorders can be treated using this vector due to such properties. rAAv is being used currently for various neurological disorders in five early stages of a clinical trial (Mandel, 2006). Channelrhodopsins (Chrs) can be targeted to specific neurons for neural circuits using genetic methods, which is also used to manipulate neuronal activities. To advance the potential in treating neurological disorders and its application. The spectral and kinetic properties of Chrs by generating variants of ChRs or exploring new rhodopsins from other species must be optimised according to the application. One of the potential of GT, ChRs through gene expression system union cell or tissue-specific promoters/enhancers should be targeted to the specific types of neurons, neurological disorders (Ji *et al.*, 2013). The study purpose that the use of RNA interferons for CDKS silencing presence attractive and specific therapeutic alternative for Alzheimer's diseases against other tauopathies. Recent technological innovations have focused on highly specific viral vector designs such as plasmids transfection, polymer mediated gene delivery, nanoparticles, engineered microRNA and in Vivo clustered regularly interspaced short Palindromic repeats(CRISPR) for improved gene sequencing delivery which is based on therapeutics which is a contrast to the present study (Pagenstecher *et al.*, 2009).

This study has limited articles compared to other articles. The experimental study is not done to prove the necessary information. This study has advancement in gene transfer for many other neurological disorders (Pena *et al.*, 2020).

CONCLUSION

GT in the coming decades may revolutionise the treatment of neurological disorders, but great challenges ahead must be faced. The over-expression of therapeutic genes emphasises the strength of GT. However, the ideal therapeutic goal in a number of dominantly inherited nervous system diseases would be to inhibit the expression of the disease causing allele. This review is an attempt to update the recent advances in gene therapy in neurological conditions, further studies in this field is required to know its complete uses to humanity.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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