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Review Article

Gene Therapy of Parkinson's Disease

Ayesha Aftab Malik

International Islamic University Islamabad, Pakistan.

Abstract | Parkinson's is second most common neurological disorder in the world having both sporadic and familial cases. Present Parkinson's disease genetics taxonomy specifies 18 chromosomal regions that are also called chromosomal locus which are termed PARK. Gene therapy i.e., Use of genes as medicine, is effective and newly discovered treatment of many Central nervous system disorders including Parkinson's disease. Direct injection was also performed but it does not give suitable results. So, scientist feel need of using different vectors for efficient delivery of genes in Central nervous system. Hence gene therapy of Parkinson's disease involves use of both viral and non-viral vectors but viral vectors shows efficient results. Frequently used vectors for therapy of Parkinson's disease are Lentivirus and adeno associated virus. Using these vectors many successful experiments are performed on different animals. Parkin, Glial cell-derived neurotrophic factor (GDNF) and alpha synuclein are some of the successful products for therapy of Parkinson's disease.

Keywords | Parkinson's disease, Genetics, Gene therapy, Lentivirus, Adeno associated virus.

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***Correspondence** | Ayesha Aftab Malik, International Islamic University Islamabad, Pakistan; **Email**: ayesha.msbt226@iiu.edu.pk
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INTRODUCTION

Parkinson's disease is a very common and widely spread neurological disorder. It is very common among people of all contests and topographical areas (Massano and Bhatia, 2012). Parkinson's disease is the second most public neurodegenerative sickness next to Alzheimer's disease (De Lau and Breteler, 2006). Symptoms are given in (Table 1).

Epidemiology and risks

Male is more prone to this disease than females. Men to women ration of Parkinson's disease is 3:2 (De Lau and Breteler, 2006). Yearly occurrence rate range is from 8.6 to 19 per 100,000 (De Lau and Breteler, 2006, Twelves et al., 2003). An occurrence of 1%-2% in the people elder than 60–65 year, or 0.3% in the over-all inhabitants (De Lau and Breteler, 2006, Hirtz et al., 2007), with frequency rates fluctuating from 65.6 to 12,500 per 100,000 population (Von Campenhausen et al., 2005). More than 4 million Parkinson's disease patients were there in the globe in year 2005 (Dorsey et al., 2006). It befalls irregularly below 40 years of age, early onset increasing the possibility that hereditary reasons might be involved (De Lau and Breteler, 2006, Schrag and Schott 2006).

Genetics

Research in Parkinson's disease shows that many monogenic form of ailments and genetics is involved in the aggregating the risk of Parkinson's disease. Monogenic forms that are initiated by a single mutation which follows dominant or recessive inherited genetics. They mutually cause 30% of the familial and it was also found in 3% to 5% of the sporadic cases. Present Parkinson's disease genetics taxonomy specifies 18 chromosomal regions that are also called chromosomal locus which are termed *PARK*. Confirmed PARK designated gene loci mode of inheritance etc. Are described in (Table 2) (Klein and Westenberger 2012).

Gene therapy: An expected treatment of Parkinson's disease

Gene therapy (use of genes as medicines) is basically used to correct defective genes responsible for genetic disorder (Miller, 1992; Verma and Weitzman, 2005). Gene medical care is the use of nucleic acids as medication (Kay et al., 2001). Thus, as for any drug, its application is going to be primarily restricted to therapeutic uses. Four classes or sorts of factor medical care are defined: (i) corporal factor gene therapy, (ii) corporal genetic enhancement, (iii) germ line factor gene therapy, and (iv) germ line genetic enhancement (Misra, 2013).

About 4,000 sicknesses have been traced which are caused by gene disorders. Modern-day and viable candidates for gene remedy consist of most cancers, AIDS, cystic fibrosis, Parkinson's and Alzheimer's sicknesses, amyotrophic lateral sclerosis (Lou Gehrig's ailment), cardiovascular ailment and arthritis https://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/gene-therapy.page?.

Table 1: Symptoms of Parkinson's disease [1].

Motor symptoms	Non-motor symptoms
Bradykinesia: Sluggish drive Loss of breadth/rapidity Reduction of muscular power(paresis) spasticity	**Neuropsychiatric features:** Anxiety, panic attacks, Mood disorder ,depression, illusion, delusion, dementia
Rest tremor	**Sleep complaint:** Insomnia restless leg syndrome behavior malady daytime drowsiness episodic limb movement during sleep
Inelasticity of muscles	**Sensory dysfunction:** Damage sense of smell decline optical contrast and hue judgment irregular sensation
Postural and gait damage: Curved posture Reduction in arm swipe Damage Mobility and turning	**Pain**

Methods of Gene Delivery to Target Cells

Non-viral Methods: Various strategies are developed for transfer of gene to the target cells that embody infective agent vectors, and non-viral systems. Non-viral strategies that are marginally used for gene transfer to the central system (CNS), comprise chemical and physical strategies, like gene gun or electroporation. The power of infective agent vectors to convert nondividing cells is of crucial importance within the context of Parkinson's disease gene medical care (Coune et al., 2012).

Research efforts have yielded many non-viral strategies cis- tron transfer like electroporation (creation of electrical field iatro- genic openings in plasma membrane), sonoporation (ultrasonic rates to disturb cell membrane), magnetofection (usage of magnetic unit complexed with DNA), cistron guns (sprouts DNA covered gold units into cells by victimization high pressure) and receptor mediate cistron transfer area unit being explored. While every methodology has its own blessings and downsides (Misra, 2013).

Table 2: Parkinson's disease *related loci nominated by PARK* [8].

Symbol	Gene locus	Gene	Inheritance
Park 1	4q21-22	*SNCA*	Autosomal dominant
Park 2	6q25.2–q27	*Parkin*	Autosomal recessive
Park 6	1p35–p36	*PINK1*	Autosomal recessive
Park 7	1p36	*DJ-1*	Autosomal recessive
Park 8	12q12	*LRRK2*	Autosomal dominant
Park 9	1p36	*ATP13A2*	Autosomal recessive
Park 10	1p32	Unknown	Risk factor
Park 14	22q13.1	*PLA2G6*	Autosomal recessive
Park 15	22q12–q13	*FBX07*	Autosomal recessive

Viral methods: Viral vectors are built from wild-type viruses by eliminating the genes, crucial to their duplication, from their genome. The vectors are thus able to infect cells and transmission their genetic material into the nucleus, however they are not able to duplicate themselves within the host cells. This side is crucial for vector safety, because it removes virus pathogenicity and stops uncontrolled dispersal of transgene delivery initiated by vector replication within the host animal.

Here we are going to target vectors derived from adenoma-associated virus (AAV) and lentivirus, as they're the sole ones that have touched the clinic for CNS citron medical aid trials (Coune et al., 2012).

Lentivectors: Lentiviruses, belong to family *Retroviridae*. They are enveloped viruses whose genome contains single stranded RNA which encodes structural proteins. Their genome consists of four genes i.e. Gag, pol, tat, and rev. The highest packaging capability of lentivectors is eighteen kilo bases (KB), however the foremost economical packaging is attained with genomes within vary of half-dozen to nine KB (Coune et al., 2012).

AAV-based vectors: Aavs belongs of family parvoviridae family. They are small and non-enveloped viruses. Their genome size is 4.7 kb AAV which contains single-stranded DNA. This DNA encoding four proteins which are very vital for replication and packaging (*rep* gene), it also encodes three capsid proteins (*cap* gene) which are enclosed by two inverted terminal repeats (ITR). AAV vectors are best vectors to transfer genes in the CNS. They provide us with very good safety profile, and effective transduction and strong expression of neurons. Beside all this there is also a limitation of AAV that is the restricted packaging volume (4.7 kb) that excludes the incorporation of huge genes (Coune et al., 2012).

Table 3: Some gene therapy approaches and their application in CNS disorders.

Gene therapy approaches	Applications	References
Anti-apoptotic genes	Delivery of anti-apoptotic gene for the treatment of Alzheimer's disease.	[18]
Gene replacement	Lentiviral vectors expressing normal SMN1 gene in models of spinal muscular atrophy.	[19]
Knockdown of gene expression	Lentiviral vectors expressing sirna targeted to mutant SOD1 gene in the model of amyotrophic lateral sclerosis.	[20]
Neurotrophic factors	Localized lentiviral mediated GDNF or DBNF delivery protects the surviving neurons from degradation in rodents'models of Parkinson disease.	[21-24]

DISCUSSION

Effective Gene Therapy Mediated Products Used for Parkinson's Disease Treatment

Parkin (Shimura, 2000) GDNF (Glial cell line-derived neurotropic factor) (Choi-Lundberg, 2015) and alpha synuclien (Maraganore, 2015) are the three-gene therapy based product of Parkinson's disease.

Glial cell line-derived neurotrophic factor (GDNF) ropes development and existence of dopaminergic (DA) neurons. Ad vector- mediated GDNF gene therapy might sluggish the DA neuronal cell harm in individuals with Parkinson's disease (Maraganore, 2015; Blömer et al., 1998; Azzouz et al., 2004; Raoul et al., 2005; Déglon et al., 2000; Kordower et al., 2000; Azzouz et al., 2004; Kirik et al., 2004).

Parkin is gene product of familial Parkinson's disease. Viral vectors for Parkin manifestation have revealed neuro-protective properties in numerous animal models of Parkinson's disease (Shimura, 2000).

CONCLUSION

Parkinson's disease is a serious CNS disorder which need treatment on urgent basis as it has many symptoms which becomes worst with the passage of time (Table 3). Its prevalence is increasing and it has both genetic and sporadic factors involved. Symptomatic therapies show no effective treatment so researched move toward gene therapy. Production of novel vectors will increase the efficiency. Different product has been designed using gene therapy for the treatment of Parkinson's disease including Parkin, GDNF and alpha synuclein. But still there is need to further research in this field especially there is strong need to implement these Products on more Humans and design new vectors and products.

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CONFLICT OF INTEREST

There is no conflict of interest.

AUTHORS CONTRIBUTION

This paper is written by Ayesha Aftab Malik, student of MS Biotechnology, International Islamic University Islamabad, Pakistan.

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