International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319 – 6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 5; May 2017; Page No. 3880-3886
DOI: http://dx.doi.org/10.24327/ijcar.2017.3886.0387

Research Article

GENETIC BASIS OF NEUROLOGICAL DISORDER WITH HUMAN INDUCED PLURIPOTENT STEM CELLS

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A R T I C L E I N F O

Article History:

Received 25th February, 2017
Received in revised form 2ndMarch, 2017
Accepted 15th April, 2017
Published online 28th May, 2017

Key words:

Rett syndrome, Autism Spectrum Disorder, hiPSCs, *COX4*, Transcriptional factors and Animal model

A B S T R A C T

Diseases related with the nervous system which include both central nervous system and peripheral nervous system and neurons are commonly called as neurological disease. If there are loss of neurons, mutation in the genes that code for neuron and their growth, differentiation, function and protein synthesis are also consider as a neurological problems. Today most of the aged people are affected with different neurological disease. They are Rett syndrome, Alzheimer's disease, Parkinson's disease, Autism Spectrum disorder, Huntington's disease and Schizophrenia. These are the neurological disease that affected major of the population. Other diseases that are associated with neurological abnormalities are Angelman Syndrome, Trimothy syndrome and William syndrome. Today it is very complex to treat neurological patients because of several ethical and social issues. Apart from this we cannot directly use animals in the experiments for research because of multiple bioethics and bio-safety issues. In order to overcome this limitations and ethical rights, several countries are producing different models such as non - human primates, mammalian model and animal models. Thus, discoveries in stem cell technology and cell cultures leads to new direction of producing neurological models for several neurological disease and disorders. The new method in stem cell technology is called human induced Pluripotent Stem Cells (hiPSCs). Using hiPSCs several disease models are produced and we can understand the molecular mechanisms of several neurological diseases.

INTRODUCTION

Non-Human Primates (NHPs) which are phylogenetically close to human beings which shows similarities in terms of physiology, anatomy, immunology and neurology are used as a experimental model in the biomedical research (Xiao-Liang Zhang *et al.,* 2014). Each and every areas of research requires the animal models which plays an important role in biomedical research (Josef van der Staay *et al.,* 2009). Animal models play a crucial role in the biomedical investigation of behaviour and of the pathophysiological process and mechanisms that are included in the control of normal and unusual behaviour (Holmes, 2003). The purpose of using animal models in the neurobehavioral disorders are (i) to understand the brain-behaviour relationship (D'Mello and Steckler, 1996) (ii) to investigate the brain damages that caused naturally or experimental induced and to study the cascade pathways (Cernak, 2005) (iii) to express the understanding of preclinical animal studies to clinical studies (Porges, 2006) (iv) to find new pathways, targets and process of drug action (Matthews and Kopczynski, 2001; Snaith and Törnell, 2002; West *et al.,* 2000) (e) to examine the risk such as safety, teratology and toxicology associated with the treatment (Bolon, 2004). Use of animal models in biomedical research helps to overcome the ethical rights on using human as experimental subjects, mainly in clinical trials (Van Der Worp *et al.,* 2010). America which is the home country for primate research institution which includes 8 National Primate Research Centres (NPRCs) funded by National Institutes of Health (NIH) that develop NHP for basic and applied studies of human health (Kaiser, 2013). Research institution of primate in America which produces non human primates is tabulated in table 1.

Table 1 List of American Institution that Develop Non-Human Primates (NHPs)

S. No.	Institutions	Reference
1	California National Primate Research Center	
2	New England Primate Research Center	
3	Southwest National Primate Researc Center	
4	Tulane National Primate Research Center	
5	Washington National Primate Research Center	
6	Wisconsin National Primate Research Center	Kaiser, 2013
7	Yerkes National Primate Research Center	
8	Oregon National Primate Research Center	

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It has totally 26,000 NHPs (Hayden, 2008). Other American Institutions that strongly focuses on NHP research and also receives federal and state funding (Wadman, 2011a). Other American Institution that focuses on NHP research is represented in the table 2. Early studies reveal that the similarity of the DNA between NHPs and human beings is 98.77% (Fujiyama *et al.,* 2012).

Table 2 Other American Institution that focuses on NHP Research

S. No.	Others institutions	Reference
1	New Iberia Research Center at the University of Louisiana at Lafayette	Wadman, 2011a
2	The University of Texas MD Anderson Cancer Center	
3	Alamogordo Primate Facility and Primate Foundation of Arizona	
4	A squirrel monkey colony of the University of South Alabama	
5	The Caribbean Primate Research Center	
6	A baboon breeding facility of the University of Oklahoma	

Human Induced Pluripotent Stem Cells (hiPSCs)

By reprogramming body cells such as blood cells, skin fibroblast, urine epithelial cell and lung cell with help of pluripotent transcription factor such as *OCT4, SOX2, c-MYC, KFL4, LIN28, NANOG* and so for most of hiPSCs are produced (Fabin Han *et al*., 2015). Understanding the neuronal diseases is a quite challenge task because of many different and connected parts are involved and the lacks of approachable techniques toward the human brain for direct observation (Park *et al*., 2008). Recent discovery in the field of stem cell technology accessed the researchers to produce hiPSCs (Yu *et al*., 2007). Today hiPSCs model are used to understand the molecular mechanism and features of neurological disease (Aaron Topol *et al*., 2015).

hiPSCs corresponds to an autologous cellular model for treatment and study different types of diseases, attainment of objectives of personal medicine. The field of personal medicine is based on the different behaviour of individuals that varies at different diseased condition. With the help of individual's clinical, genetic and environmental information, the personal medicine improves the medical care and results of modified disease prevention, diagnosis, and treatment. hiPSC corresponds with the idea of disease modelling of personal medicine and further medical application. Apart from that hiPSC also overcomes the restriction of immune rejection, patient-specific cells, merged to a 'rejuvenation' of telomere length reprogramming, epigenetic memory and functional properties (Paola Spitalieri *et al*., 2016). The major principle of using hiPSCs is to clearly explain the association between particular gene mutation, variant, epigenetic modification and expression level of particular gene (Stevens *et al*., 2012; Vaccarino *et al*., 2011).

Neuronal Diseases

Alzheimers Disease (AD)

AD is characterized by progressive neuronal loss and the accumulation of amyloid β -peptides (Aβ) in the form of extracellular plaques. AD is the most frequent cause of dementia. There are several reports which gives evidence that crowding of amyloid β peptides and proteolytic process of amyloid precursor protein (APP) plays a crucial role in pathogenesis of AD (Philipp Koch *et al*., 2012). The two pathological biomarker of AD is intraneuronal neurofibillary tangles and extracelluar senile plaque. This senile plaque composed of amyloid β peptide mainly isoforms like Aβ1-42 (Tanzi and Bertram, 2005). Early onset form of AD is mostly caused by mutation in presenilin (PSEN1, PSEN2) or amyloid precursor protein (Bertram *et al*., 2010).

Till today 36 million people are affected with AD. It is characterized by memory loss, behavioural changes because of neuronal loss and cognitive impairments (Blennow *et al*., 2006). Major risk factor for sporadic AD is ageing. It is revealed that the prevalence will be increase to 5% and 30% for 65 and 80 years old people (Ferri *et al*., 2005). Neprilysin-2 (Nep-2) is seen in brain tissue and its activity is reduced in cognitive impairment patient and AD patient (Huang *et al.,* 2012). In order to find the diagnostic method for AD, transgenic mice lines that express Aβ are used as experimental models. During clinical trials vaccination process for AD patient failed and results in several effects such as meningo-encephalitis, vasogenic edema and micro hemorrhage for some treated patients (Koutaro Takamatsu *et al*., 2014). Model used in AD such as non-mammalian model, mammalian model and human cell model (Urszula Wojda and Jacek Kuznicki, 2012). List of animal model used in AD is represented in the table 3.

Table 3 List of Model used for Alzheimer's disease

Organism	Model	Reference
Non-Mammalian Model: *Caenorhabditis elegans* *Drosophila melanogaster* *Dario rerio*	**Aβ and tau** Transgenic expression of human pathogenic APP or tau gene variants or knockout of gene orthologs	Urszula Wojda and Jacek Kuznicki, 2012
Mammalian Model: *Mus musculus*	**Aβ and tau** Transgenic expression of mutated human genes encoding APP, PS1, tau Altered expression of β-secretase or neprilysin genes Neurotrophic imbalance/expression of gene encoding neutralizing anti- NGF antibody Hypertension/induced pharmacologically or mechanically 121 Impaired insulin signaling/transgenes	
Octodon degu dogs, cats, bears, goats	Aging/natural animals	
SAMP8 mouse	Accelerated aging/spontaneous AβPP Overproduction	
Human Cell Model	Postmortem Brain Tissues Platelets and Lymphocytes Induced Pluripotent Stem Cell	

Mei-Chen Liao *et al*., 2016 adapted a method to identify the Aβ and sAPPα from single living neuronal and glial cell derived from iPSCs and they use mainly to analyse these secretion from human induced pluripotent stem cells neurons and astrocytes. By examination of iPSCs derived neuronal and glial cell, they found that different array of cell fate show increased secretion of Aβ and sAPPα and it is highly secreted by astrocytes or GABAergic neuronal fate. A recent study reveals that peripherally transplanted $CD11^{+}$ bone marrow derived monocytes have travelled into the Aβ plaque those results in modified cells. These modified cells secrete neprilysin (a proteolytic enzyme) and reduces the Aβ accumulation mice model (Lebson *et al*., 2010). Several reports states that bone marrow derived could able to change

into active mircoglial and it also clears the Aβ (Magga *et al*., 2012).

hiPSCs derived from macrophages lineage cell (iPS-ML) expressing NEP2 express the protease with AβO degrading activity that result in reduction of AβO (Koutaro Takamatsu *et al*., 2014). Nieweg *et al*., 2015 used hiPSCs to create a cell culture model (cortical neuronal model) to study the specific causes of Aβ in human synapses, human neurons and synaptic vesicle clusters. They found that there was a loss of postsynaptic AMPA receptors, loss of axonal vesicle cluster and high phosphorylation of tau protein. Thus this observation shows the deleterious action of Aβ.

Autism Specturm Disoders (ASD)

ASD is a mixed group of neurodevelopmental disorder which affect 1% of population in developing country (Newschaffer *et al*., 2007). The concordance rate ASD for monozygotic twins is between 69% - 91% (Ronald and Hoekstra, 2011). Reoccurrence of ASD in a child within the family will be 20% higher (Ozonoff *et al*., 2011).

ASD is fastest developing disorder in USA which affects 1 in 68 children every year (MMWR Surveill Summ. 2014). Environmental agents, prenatal maternal inflammation diseases and genetic factor are the important causes for ASD (Geschwind and Levitt, 2007; Dietert *et al*., 2011). SHANK3 is a gene that codes for synaptic protein SHANK3. About 0.69 to 2.21% of individuals were having deleterious mutation in the SKANK3 gene (Hélène Darville *et al*., 2016). Willemsen *et al*., 2011 shown that microdeletion in 1p21.3 whch harbor the mir137 microRNA is associated with ASD. A list model used for autism spectrum disorder is represented in the table 4.

Table 4 List of Model used for Autism Spectrum Diorders

Organism	Models	Reference
Mouse Model	Phelan–McDermid syndrome (SHANK3)	Bangash *et al.,* 2011
	Rett syndrome (MeCP2)	Moretti *et al.,* 2006
	fragile X syndrome (FMR1)	Ronesi *et al.,* 2012
	Timothy syndrome (CACNA1C)	Bader *et al.,* 2011
	Neuroligin 3 knock out mice (Non-symptomatic Autism)	Baudouin *et al.,* 2012
	Angelman (Ube3A)	Nurmi *et al.,* 2001
	Purkinje-specific knock out of TSC1	Tsai *et al.,* 2012
	chromosome-engineered mouse model for human 15q11-13	Nakatani *et al.,* 2009
	model for 16p11.2 lesion	Horev *et al.,* 2011
	22q11.2 mice lacking PTEN	Zhou *et al.,* 2009
	CNTNAP2 lacking model	Penagarikano *et al.,* 2011
	SCN1A lacking model	Han *et al.,* 2012
	Rat and Prairie vole (Rat Induced with valporic Acid)	McGraw and Young, 2010
Zebra fish	Reelin and MET genes	Rice and Curran, 2001
Songbird	CNTNAP2 gene	Alarcon *et al*., 2008
Fly (*Drosophila*)	Neurexin 1	Li et al., 2007
	Neuroligin 1	Banovic *et al.,* 2010
	Neuroligin 2	Chen *et al.,* 2012
Nematodes (*C. elegan*)	Neuroligin homolog (nlg-1)	Hunter *et al.,* 2010

It is shown that transcription factors and chromatin modifier like POU3F2 and ZNF804A and genes coding for cell adhesion proteins like NRXN1 and NLGN1 of the neuron derived from the patient specific induced pluripotent stem cell is related with ASD. Some genetic polymorphisms in TSC1, TSC2, SHANK3 and HOMER1 that involved in the metabotropic glutamate receptor (mGluR) signalling pathway is highly susceptibility to ASD (Kelleher *et al*., 2012).

Impaired electrophysiological response to the glutamatergic synapses have been seen in neurons derived from the iPSCs of individual with SHANK3 haplo insufficiency and it can be treated by introducing cDNA expression of SHANK3 (Shcheglovitov *et al.,* 2013). Fragile X syndrome model shows increased dendrites density whereas rodent model of rett syndrome and tuberous sclerosis shows decreased dendrites density (Auerbach *et al*., 2011; Penzes *et al*., 2011).

Huntington's Disease (HD)

HD is a neurodegenerative disorder and it is an autosomal dominant disorder. It is caused by the duplication of 'CAG' repeats in the HTT gene at exon 1 position. The protein encoded by the HTT gene is present in organs and tissues, mostly in brain and testis (Paola Spitalieri *et al*., 2016). The phenotypes of huntington's disease are expressed when the trinucleotide number increased more than 36. The proteins expressed by the HTT gene integrate with other proteins and lead to different biochemical functions (Tourette *et al*., 2014).

It is untreatable hereditary neurodegenerative disorders that mostly affect the people between 35 - 55 years old. It mainly affects the neuron in the striatum especially GABA medium spiny (GABA MS). It also affects the other brain parts due to disease progression (Walker, 2007). Deregulation of cellular process such as calcium haemostasis (Bezprozvanny and Hayden, 2004), mixed mitochondrial function (Quintanilla *et al*., 2013), autophagy (Aki *et al*., 2013) are relatively associated with pathology of HD. The incidences of HD range from 0.5 (Japan) to 5-7 (Europe, USA and Canada) cases per 10000 individuals (Walker, 2007).

According to Nekrasov *et al*., 2016 established iPSCs from the patient who has low expansion repeats of CAG in HTT gene and it is differentiated into GABA MS - like neurons (GMSLNs) under suitable culture. This HD GMSLNs was analysed for diseased pathology with the help of information such as mutant huntingtin protein aggregation, increased number of lysosomes/autophagosomes, nuclear indentations, and enhanced neuronal death during cell aging. Apart from this, they have identified store-operated channel and increased entry of calcium level in HD GMSLNs genotypes. They also show that EVP4593 (quinazoline derivative) decreased the number of lysosomes/autophagosomes and stored-operated channel current in HD GMSLNs. They demonstrated that there is a link between nuclear morphology and store-operated channel calcium to mutated HTT gene. They also experimental proved that EVP4593 is an anti-HD drug.

Parkinson's Disease (PD)

It is second most crucial neurodegenerative disorder and the prevalence is 1 in 1000 European population. Most reported cases of PD are sporadic and about 5 % - 10 % follows autosomal recessive or autosomal dominant pattern of inheritance in familial parkinson's disease. These two types of inheritance have different pathological appearance. The first mutated gene was *SNCA* gene that codes of Alpha-Synulcein (αSYN) which is mostly produced by Lewy bodies in different part of the barin. A mutation is discovered in Leucine-rich repeat kinase 2 (*LRRK2*) gene of the familial parkinson's disease a research group in the year 2014 and this mutation is occur in the range of 2% in the parkinson's

patients. Despite this mutation is highly seen in an ethnic group called Ashkenazi jews. Similar to *SCNA, LRRK2* gene also inherited through autosomal dominant pattern in familial parkinson's disease (Peter Reinhardt *et al*., 2013).

PD is considered as a movement disorder in man (Wen Li *et al*., 2015). PD is a disorder which makes a person very weak and infirm by damaging the part of brain especially in the dopaminergic area. They cause symptoms such as resting tremor, rigidity, and bradykinesia. The onset of these symptoms and complication is slow (Jun Peng *et al*., 2013). The most common mutation site in *LRRK2* gene is G2091 S that results in high expression of synulcein (Nguyen *et al*., 2011). The prevalence of PD in 60 years of age is estimated to be 1% - 3% (Fabin Han *et al*., 2015).

According to Peter Reinhardt *et al*., 2013 derived the induced pluripotent stem cell from the parkinson's disease patient who have LRRK2 G2091S and they have specially repaired the mutant LRRK2 alleles in order to study the relation between LRRK2 and parkinson's disease. The result showed that LRRK2 G2091S influenced dysregulation of certain gene such as *CPNE8, MAP7, UHRF2, ANXA1* and *CADPS2*. When these four genes are studied using knockout mice, it reveals that these genes are responsible for dopaminergic neurodegenerative. Despite *LRRK2* G2091S also promoted high phosphorylation of extra-cellular signal regulated kinase ½ (ERK) and transcriptional dysfunction of *CADPS2, CPNE8* and *UHRF2* was also determined by ERK activity. They suggested that PD associated phenotypes can be improved by inactivitation of ERK activity.

Table 5 List of Models used for Parkinson's disease

Animal / Fly	Model	Reference
Fly (*Drosophila Melanogaster*)	Fly Model (*Drosophila*), who expressed a transgene encoding human α-synuclein in all *Drosophila* neurons *parkin* null mutant flies model *Drosophila* PINK1 models *Drosophila* models of LRRK2 mutant-induced PD	Surendra S. Ambegaokar *et al*., 2010
Mouse	6-hydroxydopamine (6-OHDA) animal model 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model	Damien J. Ellens and Daniel K. Leventhal, 2013

Fabin Han *et al*., 2015 isolated skin fibroblast from normal person and parkinson's patients and they have generated into iPSCs by reprogramming transcriptional factors such as *COX4*, *SOX2*, *KFL4* and *c-MYC* by transfecting method. Again they induced iPSCs into neural stem cell and then into neurons followed dopamine neurons *in vitro.* Their result showed that functional defect where improved when they transplanted the induced pluripotent stem cell into straitum of 6 -hydroxydopmine (OHDA) induced rats. Apart from this, iPS derived from neural stem cell was found to be survived and united with the brain of transplanted PD rat and differentiated into dopamine neurons *in vivo*. Models used in Parkinson's disease such as fly model (*Drosophila Melanogaster)* (Surendra S. Ambegaokar *et al*., 2010) and mouse (Damien J. Ellens and Daniel K. Leventhal, 2013). List of model used for PD is tabulated in table 5.

Rett Syndrome (RTT)

RTT is one of the autism spectrum disorder is caused by mutation in X - linked MECP2 gene which encodes for transcriptional regulator methyl-CpG-binding protein 2 (MeCP2). About 12%-15% of neuronal expression of mouse genome is affected when *Mecp2* gene is mutated and this reveals that *Mecp2*-regulator can code for unrecognized synaptic protein related to schizophrenia pathogenesis (Jennifer Larimore *et al*., 2013). RTT normally affects 1 in 10000 live female births. Most common mutation in *MECP2* is *de novo* which involves C to T mutation at CpG hotspots. Most of the RTT patients in North America have nonsense (~39%) and missense (~35%) mutation in *MECP2* gene (Aaron Y.L. Cheung *et al*., 2011). Models used in RTT are knockout mice (Gaston Calfa *et al*., 2011). List of knockout mice model used in Rett syndrome are tabulated in the table 6.

Table 6 List of Model used for Rett Syndrome

Neurological disorders	Models	References
Rett Syndrome	*Mecp2* knockout mice *Mecp2* mutant mice expressing a truncated protein Cell-type specific *Mecp2* deletions or mutations Mice expressing reduced levels of *Mecp2* Mice overexpressing wildtype full-length MeCP2 Knock-in mice carrying RTT-associated *MECP2* mutations	Gaston Calfa *et al*., 2011

RTT is one of the most causes of crucial disability in girls. The characteristics features of RTT are motor, cognitive, communication skills by automatic dysfunction and a seizure disorder. Apart this it is lead to microcephaly, loss of purposeful manipulation skills, absence of speech, autistic symptoms, slow in acquiring new skills replaced by stereotyped hand movements, other movement disabilities including abnormal muscle tone, ataxia and apraxia, and seizure disorder. It consider as the first neurodevelopment disorder associated with abnormal transcription of methylated DNA (Smeets *et al.,* 2011).

Future Challenges for Hipscs Application

The major cell source for cell replacement therapy, disease modelling and regenerative medicine is human induced pluripotent stem cell. Apart from this, they have high potential of self-renewable activity and have a capability of differentiate into different stomatic stem cells. Recent discoveries in neural differentiation and transplantation methods made hiPSCs application easier and efficient. When they are compared human embryonic stem cell with human induced pluripotent stem cell, hiPSCs overcomes most limitation. The future application of hiPSCs is still exist in problem especially when they come to biosafety and ethical issues (Wen Li *et al*., 2015).

CONCLUSIONS

Neurological problems are one of the deadly and threatening diseases all over the world. It affects both male and female particularly old people. As we discussed above, human induced pluripotent stem cell are mostly used for producing different types of model such as non - mammalian primates models, animal model and mammalian models especially for neurological diseases and disorders. Abnormalities or

mutation that associated with the coding genes and nervous system then they are consider as neurological diseases. This human induced pluripotent stem cell is generated by reprogramming or deprogramming different transcriptional factors. The main objective of using hiPSCs is to clearly explain the association between particular gene mutations, variant, epigenetic modification and expression level of particular gene and their molecular mechanism. If disease models are produced using patient specific hiPSCs, it provides useful information of the diseases and genetic basis of that individual. By understanding the molecular mechanism using hiPSCs, we can easily generate anti-neurological drugs and we can specifically target the gene, protein, cell and tissue. This will help us for development of human well being. In this review, a summary of neurological disease and disorder, human induced pluripotent stem cell, hiPSCs advantage and challenges hiPSCs in future, several neurological model that are produced by hiPSCs were explained in detail. Details furnished in this review will further help in exploring more about neurological disease and advantage of human induced pluripotent stem cell.

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How to cite this article:

Vigensh, M and Balachandar, V (2017) 'Genetic Basis Of Neurological Disorder With Human Induced Pluripotent Stem Cells', *International Journal of Current Advanced Research,* 06(05), pp. 3880-3886.
DOI: http://dx.doi.org/10.24327/ijcar.2017.3886.0387

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