CHAPTER 2
REVIEW OF LITERATURE
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2.1 National & International

The α-Synuclein is a protein which is encoded by SNCA gene, belonging to the synuclein protein family with a molecular weight of about 14kD. There are three types of proteins in Synuclein family, namely, α-, β-, and γ-synuclein (72). The synuclein protein are mainly seen in brain areas like substantia nigra pars compacta, thalamus, caudate nucleus and amygdala. These synuclein proteins are seen in neuronal cells which are present in the brain and the central nervous system (CNS) also. These synuclein proteins can also be seen in hematopoietic cells, blood platelets, cardiac tissue and neuromuscular connections (73). α-Synuclein shows its activity in neural cells and is located in presynaptic nerve terminals (74).

α-Synuclein consists of 3 domains: an amphipathic N-terminal domain, a hydrophobic centre and a hydrophilic C-terminal domain. These domains will help in the α-Synuclein protein to form a α-helical, random loop formation which interacts with phospholipid-containing membranes (75,76).

The exact function of the α-Synuclein is not clear. It is highly expressed in the neuronal development (77). α-Synuclein is involved in neuronal differentiation, regulation of synaptic plasticity and regulation of dopamine release (78). α-Synuclein plays a major role in the Parkinson’s disease and also plays an important role in the etiology of several human neurodegenerative disorders like dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and amyotrophic lateral sclerosis (ALS) (79).

SNCA gene is the first one to be associated with Parkinson’s disease (3). Recent investigations have reported that three pathogenic SNCA point mutations, genomic duplications and triplications of chromosomal segments play an important role in the pathogenesis of Parkinson’s disease (80).

A Research group of Italian scientists found out the first point mutation, 209G > A A53T (Ala53Thr) in SNCA gene. This type of mutation is seen in a member of large Italian-American kindred with autosomal dominant Parkinsonism disease from Southern Italy and in three families from Greece (81,82). A similar kind of study has been conducted by some of the researchers in South Italy in the year 1990 (83).
Another research group from Department of Neurology, Medical School of Patras, Greece, has studied Clinical phenotype in patients with α-synuclein Parkinson's disease living in Greece in comparison with patients with sporadic Parkinson's disease. They have recruited 15 patients with α-syn PD and 52 consecutive patients with sPD. Their demographic data suggest that clinical severity of the disease at the time of examination did not differ significantly between patients with α-syn PD and those with sPD. They concluded that younger the age at onset of the illness, the much lower prevalence of tremor, and the longer duration of the disease characterize the clinical phenotype in this sample of patients with α-syn PD. The other symptoms and signs of the illness did not seem to differentiate the patients with α-syn PD from those with sPD (84).

In the year 1998 a study was conducted to look into the association between familial PD and SNCA. This study revealed two additional point mutations, A30P (p.Ala30Pro, c.88G>C), and another one in E46K (p.Glu46Lys, c.188G>A), in 2004 (85). It also showed triplications and duplications of the SNCA genomic locus in families with Parkinsonism. The A30P mutation was seen in only one German family with three affected members, which resulted in two additional mutation carriers who only had neurological symptoms (86). The A30P mutation has not been reported from any other family worldwide during the last 13 years except German family. In another study, E46K mutation was found in one large family with 5 affected individuals spanning two generations. This family was a native from the Basque region in Northern Spain. In the Parkinson’s disease phenotype was classified by memory dysfunction and Parkinsonism as the initial symptoms, and subsequent development of dementia. Levodopa level varies during severity of the clinical symptoms and some studies show that mutation carriers without PD symptoms revealed sleep abnormalities and cardiac sympathetic denervation (87). This type of mutation was not found in anywhere in the world.

In another study of 28 families, they have observed the rare occurrence of A53T, A30P and E46K point mutations, duplications and triplications in SNCA (88, 89). SNCA multiplications can be seen in Lister Family and it is the only one where both SNCA gene duplications and triplications occur (90).

Scientists from the Department of Neurodegenerative diseases, Herite-Institute for Clinical Brain Research in Germany, have worked on the Genetic variability in the Department of Applied Genetics, Karnatak University, Dharwad.
SNCA gene that influences α-Synuclein levels in the blood. In their study they have recruited 115 patients (mean age 64 yrs); (56 Females, 59 males). They analyzed levels of α-Synuclein in blood and brain tissue including the substantia nigra using quantitative real-time reverse transcriptase polymerase chain reaction and enzyme linked immunosorbsorbent assay in vivo. Their results showed that Single Nucleotide polymorphism (SNP) rs356219, a tagging SNP for a disease associated haplotype in the 3' region of the SNCA gene, has a significant effect on SNCA mRNA levels in the substantia nigra and the cerebellum. They have also provided the evidence that a-synuclein levels are influenced by genetic variability in the promoter and 3'region of the SNCA gene (91).

The research work conducted at Department of Clinical Neuroscience, NIHR Biomedical Research Center in London, evaluated 32 SNPs in the SNCA gene in a European Population. They had recruited 239 PD patients and 617 controls. They used 161 independently collected samples for replication. Two SNCA SNPs showed association with Multiple System Atrophy (MSA): rs3822086 and rs3775444. They reported positive genetic association between MSA and α-synuclein which has shown replication in independent samples. Their conclusive results show strongest association with cerebellar subtype of MSA (92).

A research group working in neurology department in Sacred Heart Hospital, Korea, reported mutations in PARK genes in a Korean early-onset Parkinson disease (EOPD) cohort. Sequencing was done for 35 exons of different genes SNCA, PARKIN, DJ-1, PINK1, and LRRK2. They reported PARKIN mutations in four patients with homozygous deletion of exon 2 and exon 4. In exon 4 they have reported compound heterozygous deletion and heterozygous nonsense mutation (Q40X). Four patients had PINK1 mutations; a compound heterozygous mutation (N367S and K520RfsX522) and three heterozygous mutations (G32R, R279H, and F385L). A missense mutation of SNCA (A53T) was found in a familial PD with autosomal dominant inheritance. Nine patients (12.5%) had heterozygous G2385R polymorphism of LRRK2, whereas G2019S mutation was absent. Mutations were absent in DJ-1 and UCHL1 genes. They concluded that SNCA, PARKIN, PINK1 and LRRK2 genes are genetic risk factors for PD in 25% of Korean EOPD Populations (93).
A Research group from Internal Medicine department, Federal University of Minas Gerais, Brazil studied phenotypic and genotypic characters of familial Parkinsonism and early onset Parkinson's disease (EOPD) in a Brazilian population. PRKN, PINK1, SNCA and LRRK2 genes were analyzed by sequencing method. They carried out an analysis of 575 PD, out of which 45 were IPD cases. They have identified five known mutations in PRKN, two single heterozygous and three compound heterozygous viz. P153R, T240M, 255Adel, in PRKN gene, three compound heterozygous, two single heterozygous (W54R, V31) homozygous deletion in exon 7 was observed in PINK1. In LRRK2 gene, they have identified mutation i.e. Q923H, but in SNCA gene no mutations were observed. They concluded that PRKN was the most commonly mutated gene compared to PINK1 and LRRK2 in PD (94).

Research group from Parkinson Institute, Istituto Clinici di Perfezionamento, via Bignami Milan, Italy, conducted a study on SNCA multiplication of 144 related PD patients with a positive family history. Among 144 PD patients, researchers identified one patient aged 45 years with SNCA duplication. The patient was a woman of 45 years of age with PD onset at 41 years of age. She was experiencing rapid progression of disease with early motor complications. Hence conclusion was drawn that SNCA duplication is an unusual cause of familial PD (95).

Research group of Neurologists in Neurology division, University of Saskatchewan and Saskatoon Health Region, Saskatoon, Saskatchewan, Canada, has studied role of SNCA gene in familial PD and IPD. They recruited 452 idiopathic PD cases and 245 controls. They reported allele G at rs 356165 which was associated with increased odds of PD (P = 0.013) and genetic variation in D4S3481 (Rep1) which was associated with age of disease onset. They concluded that there is a close association of SNCA gene with familial PD and IPD (96).

Research group of Mayo Clinic College of Medicine in Rochester, has studied replication and identification of susceptible genes for PD. They recruited 2692 cases and 2652 controls. They have performed genotypic technology for SNCA REP1 116 & 770 markers for individual sites. Their results show differences in SNCA Rep1 gene both in PD cases and controls. Two haplotypes were associated with PD. They concluded that SNCA Rep1 allele is associated with PD (97).
A research group of neurologists from University of Dublin, Ireland, found two novel missense mutations in Polish Parkinson's disease patients. 350 patients of Polish origin diagnosed with PD early and late onset form were recruited in their study, Direct sequencing of SNCA gene was done for the exons 3& 4 (98).

Research group from Department of Neurology, Juntendo University School of Medicine, Hongo, Tokyo, Japan, has studied the frequency of SNCA multiplications among autosomal dominant hereditary Parkinson's disease (ADPD). They had recruited 113 ADPD probands and 200 sporadic PD cases. SNCA gene was analyzed by quantitative polymerase chain reaction and fluorescence in situ hybridization (FISH) and comparative genomic hybridization array. They have reported two families (two patients from Family A and one from Family B) with SNCA duplication among ADPD patients. Their findings suggest that phenotype of SNCA multiplication may be also influenced by the range of duplication region. They concluded that, there were two newly identified Japanese patients with SNCA duplication and five previously identified American and European families with SNCA triplication or duplication mutations (99).

A Research group from Center of neuroscience and Cell biology at University of Coimbra, Portugal, has studied role of PRKN, SNCA and LRRK2 genes in Portugal populations. Out of 132 patients, 66 were considered for their study, all genes were sequenced bidirectionally, and, additionally, SNCA, PRKN and PINK1 were subjected to gene dosage analysis. They have reported mutations in LRRK2 and PRKN genes, but not in SNCA gene. Pathogenic mutations were observed in seven patients which were in homozygous type, heterozygous type of mutation was found in PRKN and another heterozygous type in LRRK2 gene (100).

Research group from Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, Center for Neurology, University of Tubingen, Tubingen, Germany, studied phenotypic variation in PD in Swedish family. This group performed alpha-synuclein sequencing, SNCA real-time PCR, chromosome 4q21 microsatellite analysis and high-resolution microarray genotyping. Their results show that a proband of the Swedish family branch presented with early dysautonomia followed by progressive Parkinsonism suggestive of multiple system atrophy. Molecular analysis identified a

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genomic duplication of α-synuclein and multimerin 1 (SNCA-MMRN1), flanked by long interspersed repeat sequences (LINE L1). Microsatellite variability within the genomic interval was identical to that previously described for a Swedish American family with an α-synuclein triplication. Subsequent genealogical investigation suggested that both kindreds are ancestrally related to the Lister family complex. They concluded that, genetic basis for familial Parkinsonism is an SNCA-MMRN11 multiplication, but whereas SNCA-MMRN1 duplication in the Swedish proband (Branch J) leads to late-onset autonomic dysfunction and Parkinsonism. SNCA-MMRN1 triplication in the Swedish American family (Branch I) leads to early-onset Parkinson disease and dementia. (101).

Another research group from Division of Clinical Genetics, Department of Medical Genetics, Osaka University Graduate School of Medicine, Yamadaoka, Osaka, Japan, has conducted a study on α-synuclein as a susceptibility gene for sporadic Parkinson’s disease. They have analyzed case-control association of 268 single nucleotide polymorphisms (SNPs) in 121 candidate genes. In two independent case-control populations, they have reported SNP in α-synuclein (SNCA), rs7684318, showing the strongest association with PD. These results conclude that SNCA expression levels tended to be positively correlated with the number of the associated allele in autopsied frontal cortices; hence SNCA gene was susceptibility for sporadic PD (102).

A research group from INSERM U289, Neurologie at Therapeutique Experimentale, Hospital de la Pitie-Salpetriere, Paris, France, has worked on causal relation between α-synuclein gene duplication and familial Parkinson’s disease. They have screened 119 individuals from families with this rare form of the disease for SNCA duplications by semi quantitative multiplex PCR. They have reported that, two patients had duplications, which were confirmed by analysis of intragenic and flanking microsatellite markers. The phenotype in both patients was indistinguishable from idiopathic Parkinson’s disease and no atypical features were observed. Their results indicate that SNCA is more frequently associated with familial Parkinson’s disease (103).

A research group from the Department of Genetics, University of New Delhi, reported the absence of G88C and G209A or any other mutations in exon 3 and exon 4 of Department of Applied Genetics, Karnatak University, Dharwad.
SNCA gene. For their study, they had recruited 169 PD Patients comprising of 18 familial, 3 Juvenile, 48 early age onset and 100 sporadic cases (104).

The research work conducted at Neurogenetics Unit, Department of Neurology, Medical School, University of Thessaly, and Larissa, Greece, evaluated the presence of SNCA and LRRK2 mutations in their populations, which comprised 55 unrelated patients with AdPD, 235 patients with sPD, and 235 ethnically matched controls, all of Greek origin. SNCA and LRRK2 mutations were analyzed by sequencing method. Quantitative duplex polymerase chain reaction of genomic DNA was also performed for patients with AdPD. Their results showed no mutations or any other multiplications in SNCA gene, but reported mutations in LRRK2 gene in two patients K544E (c.1630A > G) and A211V (c.632C > T). It was not present in controls (105).

Another research group at Neurology Service, Hospital Clinic Provincial, Barcelona, Spain, had screened for the presence of Ala53Thr mutation in the SNCA gene in Spanish Families. 34 PD patients were evaluated in their study. Out of these, 13 were early onset patients (six familial and seven sporadic). Their results showed the absence of Ala53Thr mutation in all patients. Their results did not support the role of this mutation in their patients with early onset PD (106).

Research group from the Department of Clinical Neurology, Institute of Neurology, London University, UK, has studied the absence of Ala53Thr mutation in the European populations. They concluded that Ala53Thr mutation is a very rare cause of familial Parkinson's disease (107).

Another Research group from the Department of Clinical Neurosciences, Royal Free Hospital School of Medicine, Rowland Hill Street, London University, UK., reported that G209A mutation does not play a major role in the etiology of sporadic Parkinson’s disease in the United Kingdom. They recruited 70 patients with Parkinson’s disease in their study (108).

A research group from the department of neurology, Baylor College of Medicine Houston studied G209A mutation in familial Parkinson disease in population of Non-Greek or Italian origin by recruiting 44 familial PD and 29 sporadic PD Patients. Their results suggest that none of the DNA Samples show the presence of G209A mutation.
Hence they concluded that G209A mutation is very rare in US Patients with familial PD (109).

Another Research group from Department of Medicine and Neurology, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia reported lack of Ala53Thr (exon 4) or Ala53Pro(exon 3) mutation in the SNCA gene in Chinese patients and Controls. For their study, they recruited 183 patients with Sporadic PD, 17 with younger-onset PD and 7 with familial PD as well as 273 unaffected Chinese Controls. They concluded that α-Synuclein gene is associated with PD in few families worldwide (110).

A research group from Institute for Experimental Neurobiology (Dr Gispert) and Section of Molecular Neurogenetics, University Hospital, Frankfurt, Germany has studied 190 unrelated patients with familial PD from Germany, Portugal and Yugoslavia. They have reported the absence of triplication, duplication or deletion in SNCA, LRRK2 genes among 190 cases of familial PD (111).

Research group from Department of Biology, University of Patras Medical School Patras Greece, studied SNCA G209A Mutation Carriers in Familial PD in Greece Patients. They have reported that G209A SNCA carriers are having wide phenotypic spectrum. This mutation is present in the Greece patients (112). Another research group from Department of Pathology, Hartman Institute, University of Helsinki have reported novel SNCA A53E mutation in their populations (113).

Another research group from Queen Square Brain Bank, UCL Institute of Neurology, London, UK has reported G51D SNCA mutation in British family (114). Research group from Brain Disease Center Agano Hospital Niigata Japan have studied o SNCA p.G51D mutation in early-onset Parkinson’s disease with dementia. They have reported p.G51D SNCA mutations in early-onset Parkinsonism with pyramidal signs and psychiatric symptoms (115).

Research group from Institute for Human Genetics, GSF-National Research Centre for Environment and Health, Neuherberg, Germany, revealed that, α-Synuclein gene plays a key role in the pathogenesis of both the rare familial and the common sporadic forms of Parkinson’s disease. They have studied linkage structure of α-synuclein gene region with a set of 56 genetic markers. Their results suggest that, association of

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promoter polymorphisms could not be replicated in sample set. Another set of markers in the 5'-block of the gene were also significantly associated with Parkinson's disease (116).

Research group from Department of Molecular Genetics VIB8, Flanders Interuniversity Institute for Biotechnology, University of Antwerp, Belgium, has shown that Familial Parkinson's disease (PD) has been linked to missense and genomic multiplication mutations of the α-synuclein gene (SNCA). They have also shown that the α-synuclein gene leads to susceptibility to Parkinson's disease (117).

Another research group from Department of Clinical Genetics, Erasmus MC, Rotterdam, Netherlands, has analyzed LRRK2, SNCA, Parkin, PINK1 and DJ-1 in Zambian patients with Parkinson's disease. None of these genes have got the novel mutations in above said populations (118). Research group from Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, have reported heterozygous deletions or duplications in the PARKIN gene, but they have not got the any mutations in SNCA and DJ-1 genes(119).

Research group from Qatar Foundation Annual Research Forum, has reported no SNCA mutations in their populations (120).Another research group from Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China have studied α-synuclein gene and have shown that, it is associated with Parkinson's disease. 332 PD patients and 300 healthy controls were recruited from Han Chinese populations from two centers in mainland China. Their results revealed that SNP rs7684318 (T>C) transition of the SNCA gene associated with PD in Chinese Han population (121).

Another research group from Section of Medical Genomics, Department of Clinical Genetics, VU University Medical Center, Amsterdam, Netherlands, have studied Parkin, DJ-1, PINK1, LRRK2, and SNCA genes in a Dutch EOPD Patients. They have recruited 187 unrelated Dutch EOPD patients (age at onset< or =50 years). They have reported seven novel mutations in Parkin, DJ-1, PINK1 and LRRK2 genes but they have not got any mutations in SNCA gene (122).

Many studies conducted worldwide have reported the association of NOS1 gene in PD. Research group from Section of Medical Genomics, Department of Clinical Genetics, VU University Medical Center, Amsterdam, Netherlands, have investigated the
polymorphisms present in NOS1 gene contributing to the risk of developing PD. 209 PD patients and 488 controls of European (mostly French) ancestry and matched for age, sex and region of residency were included in their study. They have observed the association of exon 22 and 29 of NOS1 gene with PD. All together, this study favours an involvement of NOS1 gene as new modifier gene in PD (123).

A research group from Department of Biotechnology, School of Bioengineering, SRM University, Kattankulathur, Tamil Nadu, India, has studied increased prospect of robust molecular definition in detection of PD through the early symptomatic phase of the disease. The study included the microarray based gene expression profiling of NOS1 gene along with the other pathway related genes. This is an ultimate opening for therapeutic intervention (124).

Research group from Inserm, U708 Neuroepidemiologie & universite Pierre-et-Marie-Curie, groupe hospitalier Pitie-Salpetriere, Paris cedex, France, reported that there is inverse association between smoking and the risk of PD. Polymorphism in the NOS1 gene is responsible for PD. Altogether, the study concluded that, the NOS1 gene plays a role in PD susceptibility. Although the exact mechanism accounting for the interaction between smoking and the genetic factors remains unclear and merits further studies, it is in favour of a protective effect of cigarette smoking for PD (125).

Research groups from University Program in Genetics and Genomics, Duke University, Durham, NC 27710, USA, has studied association of NOS1 Gene-environment interactions including caffeine, pesticides, anti-inflammatory drugs and nonsteroidal smoking. They reported that rs3782218, rs11068447, rs7295972, rs2293052, rs12829185, rs1047735, rs3741475, and rs2682826 SNPs of NOS1 gene are associated with PD. They concluded that, NOS1 gene is major genetic risk factors for PD (126).

Another research group from Human Genetics department in Miami has conducted a genome wide association study of SNPs in SNCA and the MAPT Region as Common Risk Factors for Parkinson Disease. They have reported that SNCA and MAPT region are influencing risk of PD. Their results show that, SNPs in SNCA (rs2736990) G vs. A allele, attributable risk percent (12%) and the MAPT region (rs11012) T vs. C allele, (8%) was genome-wide significant (127).
A research group from Eskitis Institute for Cellular and Molecular Therapies, Griffith University, Nathan, Australia, has studied on mutations in early-onset Parkinson's disease patients in PARK genes from Queensland, Australia. They have recruited 74 early-onset PD cases out of 950 patients (onset <50 years) for genetic abnormalities in known familial Parkinsonism genes. A self-reported family history of PD existed for 30 patients (40.5%). Of these, 13 each had a first- or a second-degree relative with PD and four reported a more distant relative with PD. Direct sequencing was carried out for PRKN, DJ-1 and PINK1 genes, and exon 41 of the LRRK2 genes. Their results show that two patients carried PRKN mutations (p.G12R heterozygous and p.G430D homozygous), one patient carried a p.G411S heterozygous amino acid change in the PINK1 gene and two individuals were heterozygous for the common p.G2019S mutation in LRRK2. No alpha-synuclein or DJ-1 variants were observed. Their findings suggest that approximately 7% of early-onset PD cases seen in Queensland movement disorders clinics have mutations involving known PARK gene (128).

Research group from Department of Neurology, Kyung Hee University College of Medicine, Korea, has studied SNCA multiplication in patients with familial and sporadic PD and multiple system atrophy (MSA). They have recruited 1,106 patients with parkinsonism (PD = 906, MSA = 200), SNCA multiplication performed by multiplex PCR. Fluorescent in situ hybridization was done to confirm the multiplication. Their results show that three patients were SNCA duplication. One patient had a positive family history, and two patients were sporadic. The study concluded that SNCA multiplication is confirmed in sporadic Parkinson disease (PD), may be one of the copies for low penetrance, clinical heterogeneity, and normal dopamine transporter imaging in asymptomatic carriers. SNCA duplication may be due to other genetic modifiers or environmental triggers (129).

A research group from Neurogenetics, Department of Neuroscience, College of Medicine, Mayo Clinic, Jacksonville, Florida, USA, has studied five families with Parkinsonism and identified the changes in chromosomal 4q21 locus containing the α-synuclein gene through microsatellite analysis. In this study the researchers have found out two genomic mechanisms which were said to be responsible for multiplications in chromosome 4q21, including both SNCA duplication and recombination. They
concluded that, SNCA dosage is responsible for Parkinsonism, autonomic dysfunction, and dementia observed within each family (130).

Another research group from Laboratory of Neurogenetics, Mayo Clinic Jacksonville, Jacksonville, USA, have investigated 50 probands with autosomal dominant Parkinsonism for α-synuclein mutation and genomic multiplications. The researchers observed that all samples were diploid with two normal copies of the SNCA; hence they concluded that α-synuclein missense mutations and SNCA genomic multiplications remain a rare cause of disease (131).

A research group from Department of Health Sciences Research, University of Milano-Bicocca, Monza, Italy, have studied on the possible joint effects of SNCA REP1 genotypes and pesticide exposures on the risk of PD. For their study they are recruited 833 case-control pairs. In multivariate analyses, both SNCA Rep1 and pesticide exposures were significantly associated with PD in younger subjects, but there were no pair wise interactions. They concluded that SNCA Rep1 genotype and herbicides have independent effects on risk of Parkinson disease (132).

Another research group from Department of Neurodegenerative Diseases, ‘Hygeia’ Hospital, Athens, Greece, have studied Genetic assessment of familial and early-onset Parkinson’s disease in a Greek population. A genetic analysis performed on 111 familial or sporadic with early-onset (<50 years, EO) PD patients for the presence of A53T SNCA mutation. Their results show only five patients being identified with the A53T SNCA mutation, two with a heterozygote dosage mutation and one with a heterozygote point mutation in the Parkin gene, and seven patients with GBA gene mutations, hence they concluded that A53T mutation in the SNCA gene is uncommon, does cause of PD in the Greek population, especially of familial EOPD with autosomal dominant inheritance (133).

Research group from University Clinic of Neurology, Skopje, Macedonia, have studied mutations G88C and G209A in alpha-synuclein (SNCA) in patients with idiopathic Parkinson’s disease. They recruited 32 patients (18 men and 14 women), with mean age of 52.7 years, with clinically verified diagnosis of idiopathic Parkinson’s disease (IPD). Control group consisted of 31 randomly selected, healthy persons, similar age, with similar gender representation without history and clinical features of IPD. They
reported no Mutations G88C in exone 3 and G209A in exone 4 from SNCA gene in any of the 32 patients with IPD. Multiplication of the number of SNCA gene copies were also not found in any of these patients, but they have got statistically significant difference between the IPD and control group with regard to the presence of deletion 4977 in mitochondrial genome as well as presence of heteroplasmia in the group of patients with IPD. They concluded that there were no mutations of G88C and G209A in SNCA in their patients with IPD. Deletion 4977 in mitochondrial genome was verified as independent significant factor (134).

Another research group from Department of Neurology, Henan Provincial People's Hospital, Zhengzhou, China, have screened 51 Chinese samples that had susceptible genes for Parkinson's disease. Analysis was carried out by PCR followed by Sequencing and the results showed two missense mutations in exon 5 of LRRK2 and exon 10 of PARK2. They concluded that no novel mutations were observed and other susceptibility genes should be studied in FPD patients in China (135).

Research group from Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland, have examined SNCA gene in 629 PD patients using direct sequencing method. In this study two novel pathogenic substitutions were observed. Due to small number of samples the pathogenicity of the A18T and A29S were not determined (136).

Another research group from Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China, have investigated 685 Chinese samples and 569 controls. They carried out Meta analysis & observed AG+GG genotypes to be higher in PD than in control samples. SNCA rs356219 is PD susceptible in a large Han Chinese population of patients. They concluded that SNCA rs356219 is susceptible for sporadic PD in China and Meta analysis results were also similar in the Asian population (137).

Research groups from Department of Psychiatry, Chang Gung Memorial Hospital, Taipei, Taiwan have conducted a research to find out the association of SNCA and LRRK2 genes with sporadic PD susceptibility. In this study 626 cases and 473 controls, were screened for 17 SNPs located on SNCA gene 16SNPs located on LRRK2 gene using Genotypic technology. Their observation revealed that two SNPs near the

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promoter region (rs2301134 and rs2301135) of SNCA which were associated with PD along haplotype block with 2 SNPs in 3' UTR (rs356221 and rs11931074) revealed evidence of association where as in LRRK2 gene, only R1628P variants out of 16 SNPs giving a marginal significant association with PD. The study concluded that genetic variants of both SNCA and LRRK2 genes are associated with sporadic PD (138).