20

SNCA Gene Multiplication: A Model Mechanism of Parkinson Disease

Kenya Nishioka[1], Owen A. Ross[2] and Nobutaka Hattori[1]
[1]*Department of Neurology, Juntendo University School of Medicine, Tokyo*
[2]*Division of Neurogenetics, Department of Neuroscience, Mayo Clinic Jacksonville FL*
[1]*Japan*
[2]*USA*

1. Introduction

Parkinson disease (PD) is caused by several pathogenic mutations in genes such as alpha-synuclein (*SNCA*; MIM#163890), Leucine-rich repeat kinase 2 (*LRRK2*; MIM#609007), PARKIN (*parkin*; MIM#602544), PTEN-induced kinase 1 (*PINK1*; MIM#608309), and DJ-1 (MIM#602533) (Farrer, 2006). The alpha-synuclein protein is also a major component of Lewy bodies (LB), the pathologic substrate that is observed in PD patients at autopsy (Spillantini et al., 1997). LB are generally localized to the mid-brain in patients with PD, however a widespread distribution of LB, including cortical regions, is seen in dementia with Lewy bodies (DLB) (Braak et al., 2003, McKeith et al., 2005). The observation of *SNCA* multiplications co-segregating with PD and dementia in families led to the hypothesis that over-expression of the alpha-synuclein protein is an important mechanism of disease. Herein, we place the gene dosage effect of *SNCA* in PD in perspective and describe the recent molecular insights underlying them.

2. *SNCA* triplication and duplication in hereditary PD

PD is the second most frequent neurodegenerative disorder following Alzheimer disease in the elderly. The main symptoms of PD are tremor, bradykinesia, and gait disturbance. PD genetics is categorized into two groups; one is sporadic PD and the other is familial PD. Familial PD has two forms; autosomal dominant heredity (ADPD) and autosomal recessive heredity (ARPD). ADPD has been observed to be caused by mutations in *SNCA* and *LRRK2*. ARPD is caused by homozygous or compound heterozygous mutations in *PARKIN*, *PINK1*, and *DJ-1*(Farrer, 2006). This review will focus on *SNCA* which is located on chromosome 4q21-22 and encodes the 140 amino acid alpha-synuclein protein. *SNCA* has three point mutations; c.88G>C (Ala30Pro), c.188G>A (Glu46Lys) and c.209G>A (Ala53Thr) (Kruger et al., 1998, Zarranz et al., 2004), but they are very rare.

SNCA duplications and triplications have also been identified as a genetic cause of ADPD. Duplication has two *SNCA* copies on one allele (50% dose increase) and triplication has three, 100 percent dose increase (Figure 1). Rarely, compound heterozygote forms (two duplication alleles) are seen as *SNCA* triplication events (Ikeuchi et al., 2008). These multiplications generate higher *SNCA* expression of mRNA and protein, the so called gene

dosage effect. Increasing the levels of protein appears to influence the clinical manifestations of PD patients. A subtle increase in alpha-synuclein expression may increase the risk of developing typical sporadic PD, whereas higher expression may cause severe forms of Parkinsonism similar to DLB. Pathologically, the burden of LB correlates with a PD or DLB clinical diagnosis, and it is still unclear whether PD and DLB are a continuum within the disease spectrum.

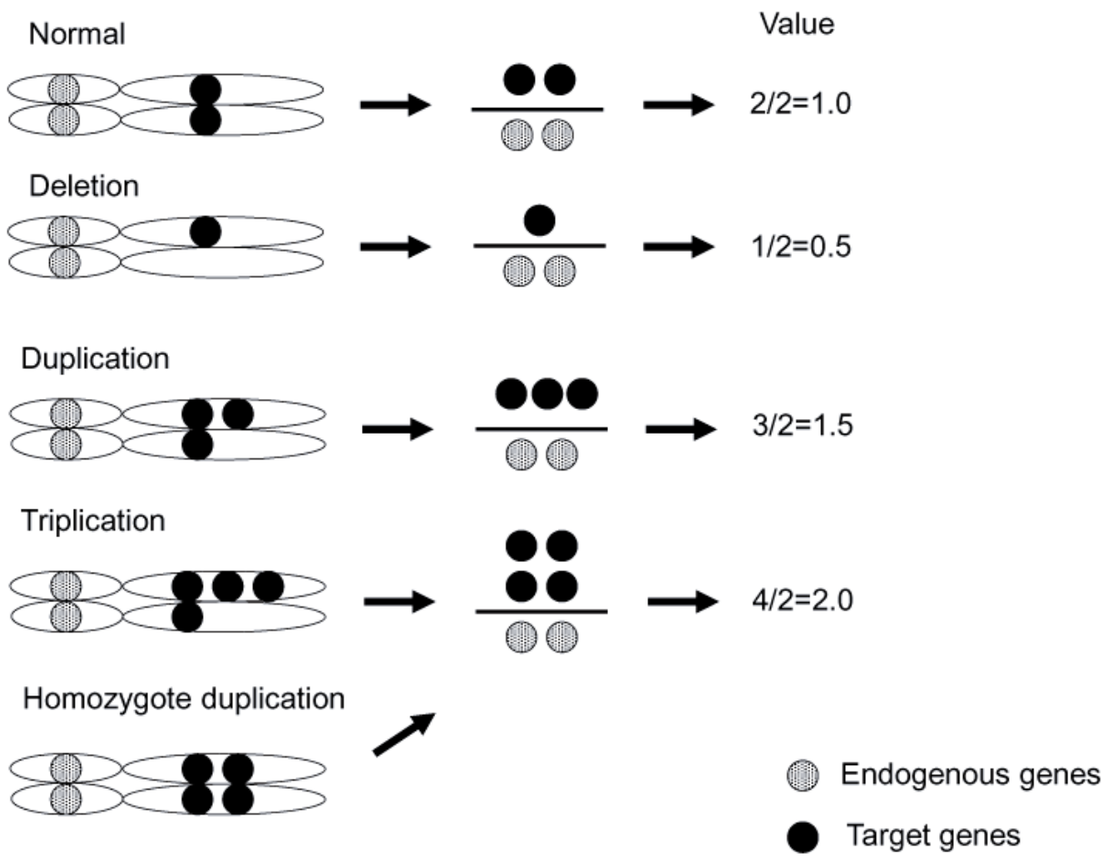


Fig. 1. A model for gene dosage of deletion, duplication and triplication

Singleton et al. first reported *SNCA* gene triplication within a large family with PD and dementia family (the Iowa kindred) (Singleton et al., 2003). The family members had been followed both clinically and pathologically by Mayo Clinic doctors for 100 years (Muenter et al., 1998, Gwinn-Hardy et al., 2000). The pattern of inheritance is autosomal dominant. The patients show a severe clinical course, early age at onset, complicating with dementia, or Parkinsonism. The pathological features are similar to DLB; (1) widespread LB pathology in the brain, (2) neuronal loss in the CA2/3, and (3) neuronal loss in the substantia nigra (Muenter et al., 1998). *SNCA* triplication was confirmed with quantitative PCR and FISH methodology. The size of the triplication region was over 2.0Mb. The expression values of messenger RNA and protein in peripheral blood and brain were twice the amount that is present in control subjects as predicted (Miller et al., 2004). Apart from the Iowan family, a

Swedish-American family was also reported as a *SNCA* triplication family and the patients had DLB-type prognosis and pathological findings. Their expression level of messenger RNA and protein of alpha-synuclein was also double the dosage of normal subjects in frontal cortex (Farrer et al., 2004).

These findings provided two novel insights regarding the underlying mechanisms of PD; (1) over-expression of alpha-synuclein may cause a more severe form of Parkinsonism such as DLB and (2) the gene dosage of alpha-synuclein may directly correlate with the clinical features of PD. Furthermore, these findings give us hints into the development of potential therapeutic avenues of treatment for PD by decreasing the expression of alpha-synuclein. The suppression of alpha-synuclein by siRNA approaches has proven successful in decreasing the levels of LB pathology in animal models (Lewis et al., 2008, McCormack et al., 2010).

After the detection of *SNCA* locus triplication, *SNCA* duplications were also reported in two families from France and Italy (Chartier-Harlin et al., 2004, Ibanez et al., 2004). Chartier-Harlin et al detected one duplication family among nine ADPD. Ibanez et al detected two families with *SNCA* duplication among 119 ADPD by 250K Affymetrix microarray and semi-quantitative PCR method(Ibanez et al., 2004). The symptoms of the patients with *SNCA* duplication are milder than that of *SNCA* triplication, younger age at onset and have a good efficacy for levodopa therapy, similar to sporadic PD.

Following these findings, we started screening for *SNCA* multiplications within 216 ADPD and 271 sporadic PD patients originating from Japan (Nishioka et al., 2006, Nishioka et al., 2009). We found six ADPD families and one sporadic case with *SNCA* duplication. Haplotype analysis showed these seven patients are derived from four common founders. Interestingly, the clinical manifestations of these patients were quite diverse such as sporadic PD, DLB-type and also many elderly asymptomatic carriers. The estimated penetrance ratio is about 30-40%. One patient presented with a severe clinical course with no efficacy for levodopa therapy. He progressed to Hoehn and Yahr stage V in a few years and at autopsy demonstrated features similar to DLB (Obi et al., 2008).

In addition, we also detected five asymptomatic carriers over 65 years old. We therefore focused our work on the reasons why the asymptomatic carriers at later ages do not present any clinical features of parkinsonism. We started to assess Brain MRI, PET study with [^{18}F]-labeled 2-fluoro-2-deoxy-D-glucose (FDG) and [^{11}C]-labeled 2β-carbomethoxy-3β-(4-flurophenyl)-tropane (CFT), polysomnography, and Sniffin' sticks to explore the differences between the patients and the asymptomatic carriers with *SNCA* duplication. Against our expectation, the assessments for asymptomatic carriers did not show any abnormal results in our studies, with similar results as those obtained for normal individuals (Nishioka et al., 2009). It is an area of intense research why the asymptomatic carriers do not develop Parkinsonism at these late ages and its resolution will be a key in the puzzle regarding the late-onset of PD.

Apart from our cases, other teams have reported two families from Japan with *SNCA* duplication (Ikeuchi et al., 2008, Uchiyama et al., 2008). Interestingly, one family has both heterozygote and homozygote duplication (producing a pseudo-triplication) (Ikeuchi et al., 2008). The clinical features of the individual with the *SNCA* homozygote duplication showed severe Parkinsonism similar to that of a triplication carrier. These findings also confirm the gene dosage effect within the same family. Earlier studies had reported that the

Swedish family named the "Lister family complex" has both *SNCA* duplication and triplication patients within different branches of the pedigree suggesting a primary duplication event followed later by another resulting in the triplication (Fuchs et al., 2007). In this family also the patient with *SNCA* triplication presented with more severe symptoms than the patients with duplication. Recently one small pedigree with SNCA triplication was detected in Japan (Sekine et al., 2010).

The breakpoint of *SNCA* multiplication is different in each family. The largest multiplication about 4.9Mb is detected within a French family. The smallest one about 0.2 Mb is in a Japanese family (Nishioka et al., 2009). The size and gene make-up of each multiplication region does not seem to influence the clinical presentation of the carrier. The single common determining factor that appears between all patients with *SNCA* multiplication is the presence of the entire *SNCA* gene. To conclude, it is clear that *SNCA* multiplication alone is sufficient to result in the parkinsonian phenotype.

2.1 Sporadic PD and *SNCA* duplication

In 2007, Ahn et al reported two sporadic patients with *SNCA* duplication from a screen of 906 PD patients (Ahn et al., 2008). The age at onset was 65 and 50 years old for the two patients. Their clinical course was similar to typical sporadic PD without severe progression or cognitive decline. The estimated penetrance ratio was 33.3% among the Korean patients. Our studies have also detected one sporadic patient with *SNCA* duplication and this means that the low penetrance *SNCA* duplications may give the appearance of sporadic disease.

2.2 The frequency of *SNCA* multiplications in PD

The prevalence of *SNCA* multiplications is relatively low (table 1). Bruggemann et al reported one sporadic case among 403 PD cases from Germany (1/403=0.25%) (Brueggemann et al., 2008). Troiano et al reported one sporadic cases among 101 young onset PD cases from French (1/101=1%) (Troiano et al., 2008). Nuytemans et al reported one duplication patient with dementia among 219 sporadic PD cases from Belgium (Nuytemans et al., 2009). Sironi et al reported one duplication patient with dementia among 144 PD cases from Italy (1/144=0.7%) (Sironi et al., 2009). Furthermore some reports did not detect *SNCA* duplication; 0/50 and 0/290 (Hope et al., 2004, Xiromerisiou et al., 2007). To conclude, *SNCA* multiplication is not a common cause of sporadic or hereditary PD.

2.3 *SNCA* multiplications in multiple system atrophy

Multiple system atrophy (MSA) is characterized by specific clinical features such as Parkinsonism, autonomic dysfunction, poor response to levodopa therapy, and cerebellar ataxia (Wenning et al., 2004). Glial cytoplasmic inclusions (GCIs) are the pathologic hallmark of the disease. As alpha-synuclein is a major protein component of GCIs, MSA is categorized within the group of neurodegenerative disorders classified as the alpha-synucleinopathies. Interestingly common variation at the *SNCA* locus has been associated with MSA risk (Scholz et al., 2009, Ross et al., 2010). Two studies did not identify any *SNCA* multiplications in a combined total of 258 MSA patients (Lincoln et al., 2007, Ahn et al., 2008). Although the number of assessed samples may be small, these findings suggest that *SNCA* dosage is not a common cause of MSA. It is speculated that PD or DLB may be cause by lysosomal dysfunction, however, MSA may be caused by the oligodendrocytic changes in myelin basic protein (Wenning et al., 2008).

	Country	The number of pedigrees	The number of screening samples	Frequency (%)	Average ot age at onset
SNCA duplication in AD cases					
Nishioka et al. 2006 and 2009	Japan (Juntendo)	6	487	1.2	48.2
Ibanez et al. 2004 and 2009	France and Italy	4	286	1.4	43.6
Sironi et al. 2009	Italy	1	144	0.7	41
Ikeuchi et al. 2008	Japan (Niigata)	1			57
Uchiyama et al. 2008	Japan (Niigata)	1			60
Fuchs et al. 2007	Sweden (Lister complex)	1			71
Ahn et al. 2007	Korea	1	906	0.1	40
Chartier-Harliln et al. 2004	France	1	9	11	50.8
total average					51.5
SNCA duplication in sporadic cases					
Nishioka et al. 2009	Japan (Juntendo)	1	487	0.2	31
Nuytemans et al.2009	Belgium	1	219	0.5	71
Brueggemann et al. 2008	Germany	1	403	0.3	36
Troiano et al. 2008	France	1	101	1	35
Ahn et al. 2007	Korea	2	906	0.2	57.5
total average					46.1
SNCA triplication					
Sekine et al. 2010	Japan (Juntendo)	1			37
Ibanez et al. 2009	France	1	286	0.3	42
Fuchs et al. 2007	Sweden (Lister complex)	1			
Farrer et al. 2004	Swedish-American	1			31
Singlton et al. 2003	Iowa	1			33.2
SNCA homozygote duplication					
Ikeuchi et al. 2008	Japan (Niigata)	1			28
total average					32.9

Table 1. The clinical manifestations and prevalence of *SNCA* duplication and triplication

2.4 The Synuclein family in Parkinson disease

The *SNCA* gene is located on chromosome 4q21-22 and is associated with susceptibility to PD and DLB. Alpha-synclein has two paralogous genes, beta- (*SNCB*; MIM#602569) and gamma-synuclein (*SNCG*; MIM#602998) with which it shares a highly conserved N-terminal domain. *SNCB* is located on chromosome 5q35, and *SNCG* is located on chromosome 10q23 associated with breast and ovarian cancer (Ji et al., 1997, Goedert, 2001). All three synuclein genes are highly expressed in brain; thalamus, substantia nigra, caudate nucleus, and amygdala (Lavedan, 1998, Lavedan et al., 1998). A phylogenic tree indicates that alpha- and beta- synucleins are related more closely to each other than to gamma-synuclein (Lavedan, 1998). Interestingly, two putative pathogenic mutations in *SNCB* are reported to cause DLB, however no significant co-segregation with disease could be shown and no other studies have identified these variants (Ohtake et al., 2004). A murine model with over-expressed gamma-synuclein is reported as a PD model with motor deficits (Ninkina et al., 2009). Our recent studies on common variation in the synuclein family of genes also suggested association for variants in both *SNCA* and *SNCG* with diffuse LB disease (Nishioka et al., 2010). Given these findings, it is postulated that there is a connection between not only *SNCA*, but also *SNCB* and *SNCG* and susceptibility to PD, however multiplications of the *SNCB* and *SNCG* loci have not yet been observed.

3. Conclusion and future work

Research focused on copy number variation has made remarkable progress in recent years. Genome-wide studies for copy number variants (CNV) indicate 1447 copy number variable regions (CNVRs) (Redon et al., 2006). Presumably, many of these CNV polymorphisms result in differential expression levels of proteins and dictate the phenotypic presentation at the individual level. Interestingly in Alzheimer disease multiplications of the *APP* gene have also been identified in families with autosomal dominantly inherited forms of the disease (Cabrejo et al., 2006, Rovelet-Lecrux et al., 2006). Robust and comprehensive studies are now warranted for CNV across the genome and may not only help develop new treatments for PD but perhaps several other neurodegenerative diseases.

4. Reference

Ahn TB, Kim SY, Kim JY, Park SS, Lee DS, Min HJ, Kim YK, Kim SE, Kim JM, Kim HJ, Cho J, Jeon BS (2008) alpha-Synuclein gene duplication is present in sporadic Parkinson disease. Neurology 70:43-49.

Braak H, Rub U, Gai WP, Del Tredici K (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110:517-536.

Brueggemann N, Odin P, Gruenewald A, Tadic V, Hagenah J, Seidel G, Lohmann K, Klein C, Djarmati A (2008) Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. Neurology 71:1294; author reply 1294.

Cabrejo L, Guyant-Marechal L, Laquerriere A, Vercelletto M, De la Fourniere F, Thomas-Anterion C, Verny C, Letournel F, Pasquier F, Vital A, Checler F, Frebourg T, Campion D, Hannequin D (2006) Phenotype associated with APP duplication in five families. Brain 129:2966-2976.

Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destee A (2004) Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet 364:1167-1169.

Farrer M, Kachergus J, Forno L, Lincoln S, Wang DS, Hulihan M, Maraganore D, Gwinn-Hardy K, Wszolek Z, Dickson D, Langston JW (2004) Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol 55:174-179.

Farrer MJ (2006) Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet 7:306-318.

Fuchs J, Nilsson C, Kachergus J, Munz M, Larsson EM, Schule B, Langston JW, Middleton FA, Ross OA, Hulihan M, Gasser T, Farrer MJ (2007) Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. Neurology 68:916-922.

Goedert M (2001) Alpha-synuclein and neurodegenerative diseases. Nat Rev Neurosci 2:492-501.

Gwinn-Hardy K, Mehta ND, Farrer M, Maraganore D, Muenter M, Yen SH, Hardy J, Dickson DW (2000) Distinctive neuropathology revealed by alpha-synuclein antibodies in hereditary parkinsonism and dementia linked to chromosome 4p. Acta Neuropathol (Berl) 99:663-672.

Hope AD, Myhre R, Kachergus J, Lincoln S, Bisceglio G, Hulihan M, Farrer MJ (2004) Alpha-synuclein missense and multiplication mutations in autosomal dominant Parkinson's disease. Neuroscience letters 367:97-100.

Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, Agid Y, Durr A, Brice A (2004) Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 364:1169-1171.

Ikeuchi T, Kakita A, Shiga A, Kasuga K, Kaneko H, Tan CF, Idezuka J, Wakabayashi K, Onodera O, Iwatsubo T, Nishizawa M, Takahashi H, Ishikawa A (2008) Patients homozygous and heterozygous for SNCA duplication in a family with parkinsonism and dementia. Archives of neurology 65:514-519.

Ji H, Liu YE, Jia T, Wang M, Liu J, Xiao G, Joseph BK, Rosen C, Shi YE (1997) Identification of a breast cancer-specific gene, BCSG1, by direct differential cDNA sequencing. Cancer Res 57:759-764.

Kruger R, Kuhn W, Muller T, Woitalla D, Graeber M, Kosel S, Przuntek H, Epplen JT, Schols L, Riess O (1998) Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet 18:106-108.

Lavedan C (1998) The synuclein family. Genome Res 8:871-880.

Lavedan C, Leroy E, Torres R, Dehejia A, Dutra A, Buchholtz S, Nussbaum RL, Polymeropoulos MH (1998) Genomic organization and expression of the human beta-synuclein gene (SNCB). Genomics 54:173-175.

Lewis J, Melrose H, Bumcrot D, Hope A, Zehr C, Lincoln S, Braithwaite A, He Z, Ogholikhan S, Hinkle K, Kent C, Toudjarska I, Charisse K, Braich R, Pandey RK, Heckman M, Maraganore DM, Crook J, Farrer MJ (2008) In vivo silencing of alpha-synuclein using naked siRNA. Mol Neurodegener 3:19.

Lincoln SJ, Ross OA, Milkovic NM, Dickson DW, Rajput A, Robinson CA, Papapetropoulos S, Mash DC, Farrer MJ (2007) Quantitative PCR-based screening of alpha-synuclein

multiplication in multiple system atrophy. Parkinsonism & related disorders 13:340-342.

McCormack AL, Mak SK, Henderson JM, Bumcrot D, Farrer MJ, Di Monte DA (2010) Alpha-synuclein suppression by targeted small interfering RNA in the primate substantia nigra. PLoS One 5:e12122.

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65:1863-1872.

Miller DW, Hague SM, Clarimon J, Baptista M, Gwinn-Hardy K, Cookson MR, Singleton AB (2004) Alpha-synuclein in blood and brain from familial Parkinson disease with SNCA locus triplication. Neurology 62:1835-1838.

Muenter MD, Forno LS, Hornykiewicz O, Kish SJ, Maraganore DM, Caselli RJ, Okazaki H, Howard FM, Jr., Snow BJ, Calne DB (1998) Hereditary form of parkinsonism--dementia. Ann Neurol 43:768-781.

Ninkina N, Peters O, Millership S, Salem H, van der Putten H, Buchman VL (2009) Gamma-synucleinopathy: neurodegeneration associated with overexpression of the mouse protein. Human molecular genetics 18:1779-1794.

Nishioka K, Hayashi S, Farrer MJ, Singleton AB, Yoshino H, Imai H, Kitami T, Sato K, Kuroda R, Tomiyama H, Mizoguchi K, Murata M, Toda T, Imoto I, Inazawa J, Mizuno Y, Hattori N (2006) Clinical heterogeneity of alpha-synuclein gene duplication in Parkinson's disease. Ann Neurol 59:298-309.

Nishioka K, Ross OA, Ishii K, Kachergus JM, Ishiwata K, Kitagawa M, Kono S, Obi T, Mizoguchi K, Inoue Y, Imai H, Takanashi M, Mizuno Y, Farrer MJ, Hattori N (2009) Expanding the clinical phenotype of SNCA duplication carriers. Mov Disord 24:1811-1819.

Nishioka K, Wider C, Vilarino-Guell C, Soto-Ortolaza AI, Lincoln SJ, Kachergus JM, Jasinska-Myga B, Ross OA, Rajput A, Robinson CA, Ferman TJ, Wszolek ZK, Dickson DW, Farrer MJ (2010) Association of alpha-, beta-, and gamma-Synuclein with diffuse lewy body disease. Archives of neurology 67:970-975.

Nuytemans K, Meeus B, Crosiers D, Brouwers N, Goossens D, Engelborghs S, Pals P, Pickut B, Van den Broeck M, Corsmit E, Cras P, De Deyn PP, Del-Favero J, Van Broeckhoven C, Theuns J (2009) Relative contribution of simple mutations vs. copy number variations in five Parkinson disease genes in the Belgian population. Human mutation 30:1054-1061.

Obi T, Nishioka K, Ross OA, Terada T, Yamazaki K, Sugiura A, Takanashi M, Mizoguchi K, Mori H, Mizuno Y, Hattori N (2008) Clinicopathologic study of a SNCA gene duplication patient with Parkinson disease and dementia. Neurology 70:238-241.

Ohtake H, Limprasert P, Fan Y, Onodera O, Kakita A, Takahashi H, Bonner LT, Tsuang DW, Murray IV, Lee VM, Trojanowski JQ, Ishikawa A, Idezuka J, Murata M, Toda T, Bird TD, Leverenz JB, Tsuji S, La Spada AR (2004) Beta-synuclein gene alterations in dementia with Lewy bodies. Neurology 63:805-811.

Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, Fiegler H, Shapero MH, Carson AR, Chen W, Cho EK, Dallaire S, Freeman JL, Gonzalez JR, Gratacos M, Huang J, Kalaitzopoulos D, Komura D, MacDonald JR, Marshall CR, Mei R, Montgomery L, Nishimura K, Okamura K, Shen F, Somerville MJ, Tchinda J, Valsesia A, Woodwark C, Yang F, Zhang J, Zerjal T, Armengol L, Conrad DF, Estivill X, Tyler-Smith C, Carter NP, Aburatani H, Lee C, Jones KW, Scherer SW, Hurles ME (2006) Global variation in copy number in the human genome. Nature 444:444-454.

Ross OA, Vilarino-Guell C, Wszolek ZK, Farrer MJ, Dickson DW (2010) Reply to: SNCA variants are associated with increased risk of multiple system atrophy. Ann Neurol 67:414-415.

Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerriere A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D (2006) APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet 38:24-26.

Scholz SW, Houlden H, Schulte C, Sharma M, Li A, Berg D, Melchers A, Paudel R, Gibbs JR, Simon-Sanchez J, Paisan-Ruiz C, Bras J, Ding J, Chen H, Traynor BJ, Arepalli S, Zonozi RR, Revesz T, Holton J, Wood N, Lees A, Oertel W, Wullner U, Goldwurm S, Pellecchia MT, Illig T, Riess O, Fernandez HH, Rodriguez RL, Okun MS, Poewe W, Wenning GK, Hardy JA, Singleton AB, Del Sorbo F, Schneider S, Bhatia KP, Gasser T (2009) SNCA variants are associated with increased risk for multiple system atrophy. Ann Neurol 65:610-614.

Sekine T, Kagaya H, Funayama M, Li Y, Yoshino H, Tomiyama H, Hattori N (Clinical course of the first Asian family with Parkinsonism related to SNCA triplication. Mov Disord 25:2871-2875.2010).

Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003) alpha-Synuclein locus triplication causes Parkinson's disease. Science 302:841.

Sironi F, Trotta L, Antonini A, Zini M, Ciccone R, Della Mina E, Meucci N, Sacilotto G, Primignani P, Brambilla T, Coviello DA, Pezzoli G, Goldwurm S (2009) alpha-Synuclein multiplication analysis in Italian familial Parkinson disease. Parkinsonism & related disorders.

Troiano AR, Cazeneuve C, Le Ber I, Bonnet AM, Lesage S, Brice A (2008) Re: Alpha-synuclein gene duplication is present in sporadic Parkinson disease. Neurology 71:1295; author reply 1295.

Uchiyama T, Ikeuchi T, Ouchi Y, Sakamoto M, Kasuga K, Shiga A, Suzuki M, Ito M, Atsumi T, Shimizu T, Ohashi T (2008) Prominent psychiatric symptoms and glucose hypometabolism in a family with a SNCA duplication. Neurology 71:1289-1291.

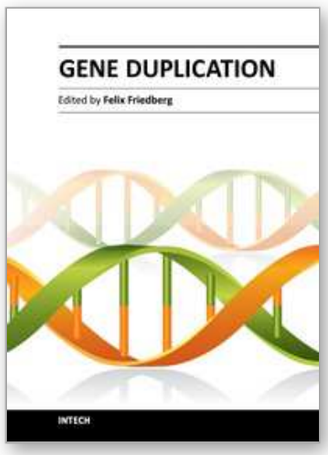
Wenning GK, Colosimo C, Geser F, Poewe W (2004) Multiple system atrophy. Lancet Neurol 3:93-103.

Wenning GK, Stefanova N, Jellinger KA, Poewe W, Schlossmacher MG (2008) Multiple system atrophy: a primary oligodendrogliopathy. Ann Neurol 64:239-246.

Xiromerisiou G, Hadjigeorgiou GM, Gourbali V, Johnson J, Papakonstantinou I, Papadimitriou A, Singleton AB (2007) Screening for SNCA and LRRK2 mutations

in Greek sporadic and autosomal dominant Parkinson's disease: identification of two novel LRRK2 variants. Eur J Neurol 14:7-11.

Zarranz JJ, Alegre J, Gomez-Esteban JC, Lezcano E, Ros R, Ampuero I, Vidal L, Hoenicka J, Rodriguez O, Atares B, Llorens V, Gomez Tortosa E, del Ser T, Munoz DG, de Yebenes JG (2004) The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 55:164-173.



Gene Duplication

Edited by Prof. Felix Friedberg

ISBN 978-953-307-387-3
Hard cover, 400 pages
Publisher InTech
Published online 17, October, 2011
Published in print edition October, 2011

The book Gene Duplication consists of 21 chapters divided in 3 parts: General Aspects, A Look at Some Gene Families and Examining Bundles of Genes. The importance of the study of Gene Duplication stems from the realization that the dynamic process of duplication is the "sine qua non" underlying the evolution of all living matter. Genes may be altered before or after the duplication process thereby undergoing neofunctionalization, thus creating in time new organisms which populate the Earth.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Kenya Nishioka, Owen A. Ross and Nobutaka Hattori (2011). SNCA Gene Multiplication: A Model Mechanism of Parkinson Disease, Gene Duplication, Prof. Felix Friedberg (Ed.), ISBN: 978-953-307-387-3, InTech, Available from: http://www.intechopen.com/books/gene-duplication/snca-gene-multiplication-a-model-mechanism-of-parkinson-disease

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen