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Mitochondrial Haplogroups Associated with Japanese Parkinson's Patients

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1. Introduction

Mitochondria are essential cytoplasmic organelles generating cellular energy in the form of adenosine triphosphate by oxidative phosphorylation. Most cells contain hundreds of mitochondria, each of which has several mitochondrial DNA (mtDNA) copies, so each cell contains thousands of mtDNA copies. mtDNA has a very high mutation rate, and when a mutation occurs the cell initially contains a mixture of wild-type and mutant mtDNAs, a situation known as heteroplasmy. If the percentage of mutant mtDNA increases enough that the cell's ATP production falls below the level needed for normal cell function, disease symptoms appear and become progressively worse. A wide variety of diseases—such as Parkinson's disease (PD), Alzheimer's disease (AD), and cancer—are reportedly linked to mitochondrial dysfunction, and it is clear that mitochondrial diseases encompass an extraordinary assemblage of clinical problems (Wallace 1999; Vila and Przedborski 2003; Taylor and Turnbull 2005).

Although mtDNA mutations have been reported to be related both to a wide variety of diseases and aging (Lin *et al.* 1992; Schoffner *et al.* 1993; Kosel *et al.* 1994; Mayr-Wohlfart *et al.* 1996; Schnopp *et al.* 1996; Simon *et al.* 2000; Tanaka *et al.* 2002; Dawson and Dawson 2003; Ross *et al.* 2003; Lustbader *et al.* 2004; Niemi *et al.* 2005; Alexe *et al.* 2007; Fuku *et al.* 2007; Chinnery *et al.* 2008; Kim *et al.* 2008; Maruszak *et al.* 2008; Feder *et al.* 2008), there are few reports regarding the relations between all mtDNA mutations and either disease patients or centenarians. The previous reports have also focused on mutations causing amino acid replacements in mitochondrial proteins and, although mitochondrial functions can of course be affected directly by amino acid replacements, they can also be affected indirectly by mutations in mtDNA control regions. It is therefore important to examine the relations between all mtDNA mutations and disease patients or centenarians.

In the article reported here the relations between Japanese PD patients and their mitochondrial single nucleotide polymorphism (mtSNP) frequencies were analyzed using a method based on radial basis function (RBF) networks (Poggio and Girosi 1990; Wu and McLarty 2000) and a modified method based on RBF network predictions (Takasaki 2009). In addition, the relations between the haplogroups of the PD patients and those of the other four classes of people (centenarians, AD patients, T2D patients, and healthy non-obese young males) are also

described using the same analysis method. The results described here are quite different from those reported previously (Saxena *et al.* 2006; Alexe *et al.* 2007; Fuku *et al.* 2007; Bilal *et al.* 2008).

2. Materials and methods

2.1 mtSNPs

We used complete mtDNA sequences available in GiiB Human Mitochondrial Genome Polymorphism Database (<http://mitsnp.tmg.or.jp/mitsnp>). The mtSNPs used were those in 96 Japanese PD patients (43 males and 53 females), 96 Japanese centenarians (30 males and 66 females), 96 Japanese AD patients (20 males and 76 females), 96 Japanese type 2 diabetes (T2D) patients (54 males and 42 females), and 96 Japanese healthy non-obese young males (Tanaka *et al.* 2004).

2.2 RBF-based method of mtSNP classification

A RBF network is an artificial network used in supervised learning problems such as regression, classification, and time series prediction. In supervised learning a function is inferred from examples (training set) that a teacher supplies. The elements in the training set are paired values of the independent (input) variable and dependent (output) variable.

The RBF network shown in Fig. 1 was learned from the training set as the mtSNPs of the PD patients were regarded as correct and the mtSNPs of other four classes of people (centenarians, AD patients, T2D patients, and healthy non-obese young males) were regarded as incorrect. Similarly, in the mtSNP classification for the centenarians the mtSNPs of the centenarians are regarded as correct and those of the other four classes are regarded as incorrect. The mtSNPs of the AD patients, T2D patients, and healthy non-obese young males were also classified this way.

The mitochondrial genome sequences of the PD patients were partitioned into two sets: training data comprising the sequences of 64 of the PD patients, and validation data comprising the sequences of the other 32 PD patients. The training and validation steps are described in detail elsewhere (Takasaki *et al.* 2006).

2.3 Modified classification method based on probabilities predicted by the RBF network

Since a RBF network can predict the probabilities that persons with certain mtSNPs belong to certain classes (e.g., PD patients, centenarians, AD patients, T2D patients, or healthy non-obese young males), these predicted probabilities are used to identify mtSNP features. By examining the relations between individual mtSNPs and the persons with high predicted probabilities of belonging to one of these classes, we are able to identify other mtSNPs useful for distinguishing between the members in different classes. A modified classification method based on the probabilities predicted by the RBF network was thus carried out in the following way (Takasaki 2009).

1. Select the analysis target class (i.e., PD patients, centenarians, AD patients, T2D patients, or healthy non-obese young males).
2. Rank individuals according to their predicted probabilities of belonging to the target class.
3. Either select individuals whose probabilities are greater than a certain value or select the desired number of individuals from the top, and set them as a modified cluster.

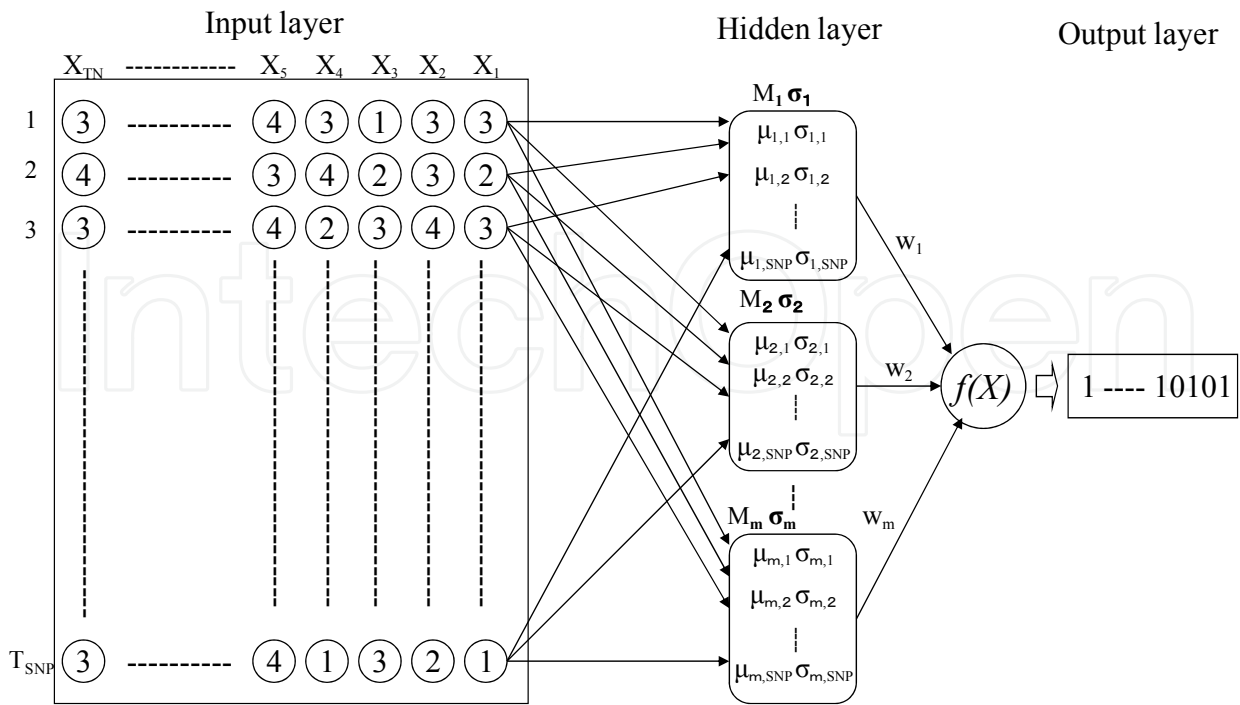
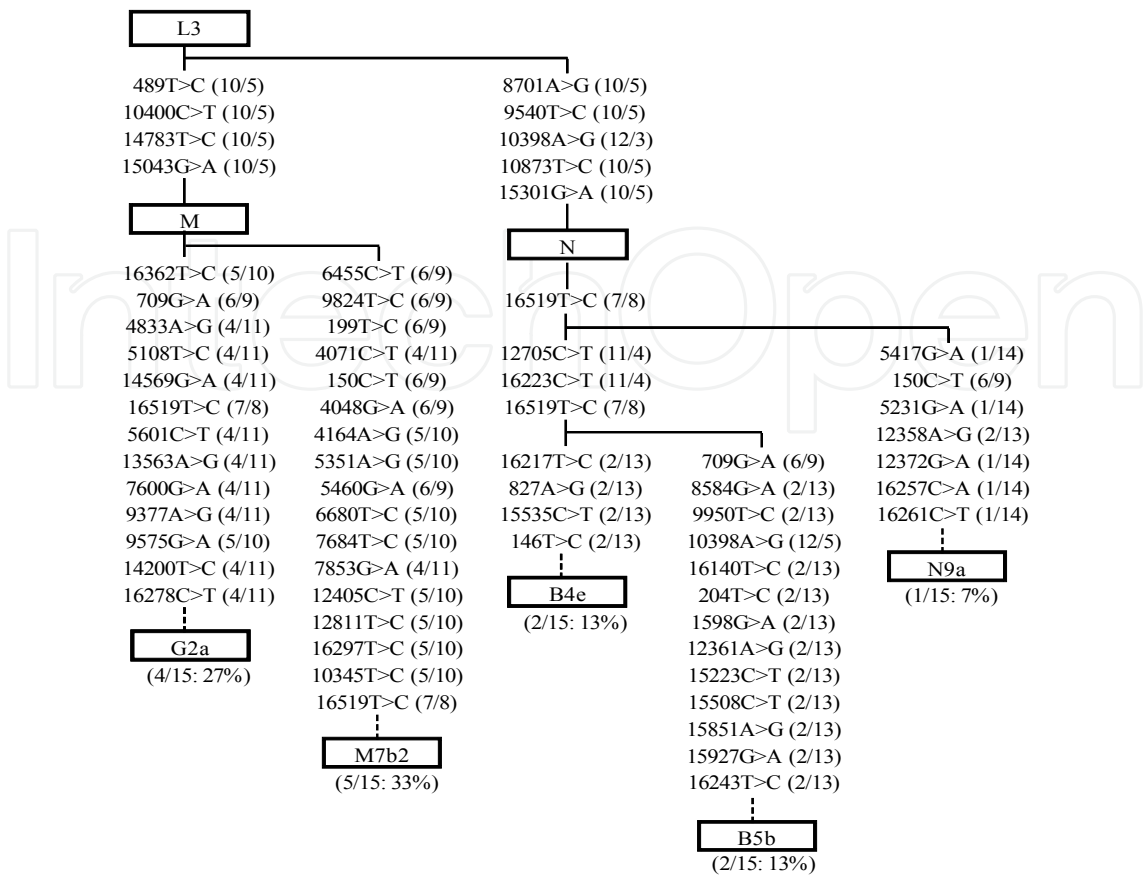


Fig. 1. RBF network representation of the relations between individual mtSNPs and the PD patients. The input layer is the set of mtSNP sequences represented numerically (A, G, C, and T are converted to 1, 2, 3, and 4). The hidden layer classifies the input vectors into several clusters depending on the similarities of individual input vectors. The output layer is determined depending on which analysis is carried out. In the case of PD patients, 1 corresponds to PD patients and 0 corresponds to other four classes of people. In the case of centenarians, 1 corresponds to centenarians and 0 corresponds to other four classes of people. The AD patients, T2D patients, and healthy non-obese young males are also carried out in similar way. X_i : i -th input vector, TN : maximum number of vectors (in this example, $TN=320$ (64x5)), T_{SNP} : maximum number of mtSNPs (in this example, $T_{SNP}=562$), M_m : the location vector, m : the number of basis functions, μ : basis function, σ : standard deviation, w_i : i -th weighting variable, $f(X)$: weighted sum function.

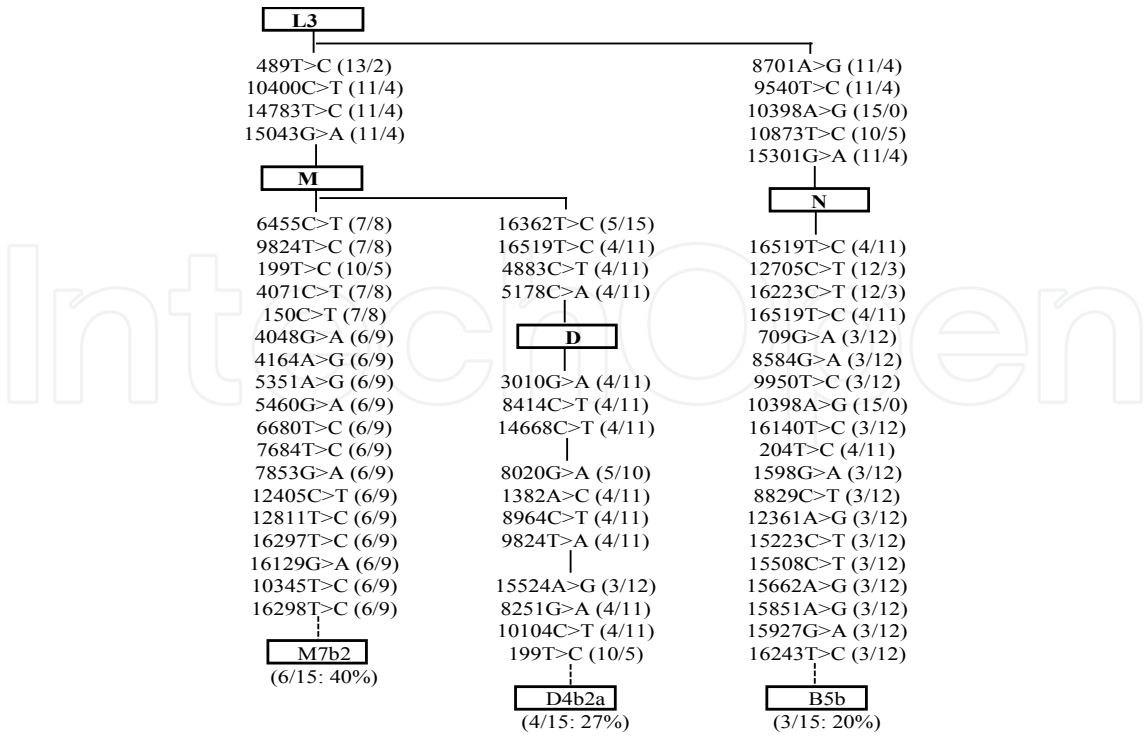
3. Results and discussion

3.1 Associations between haplogroups and the mtSNPs of the PD patients

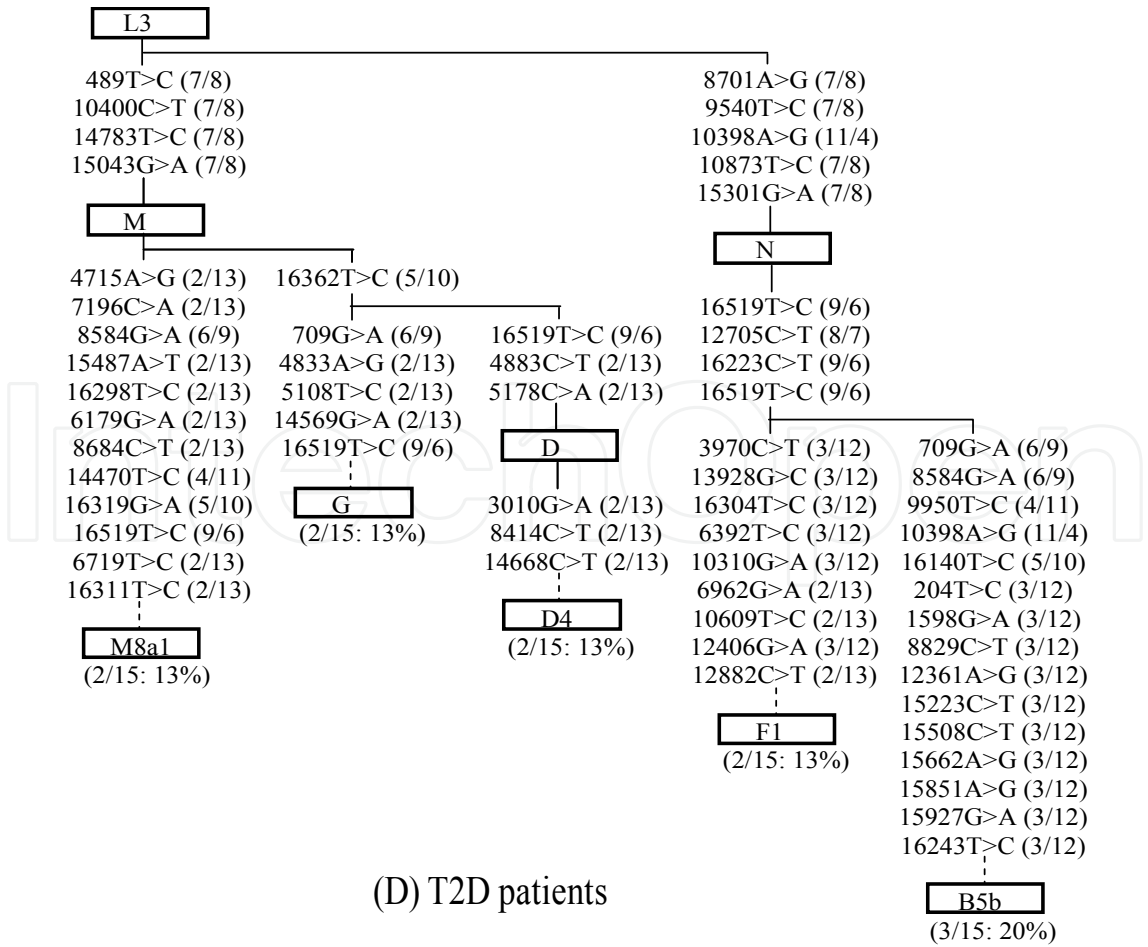
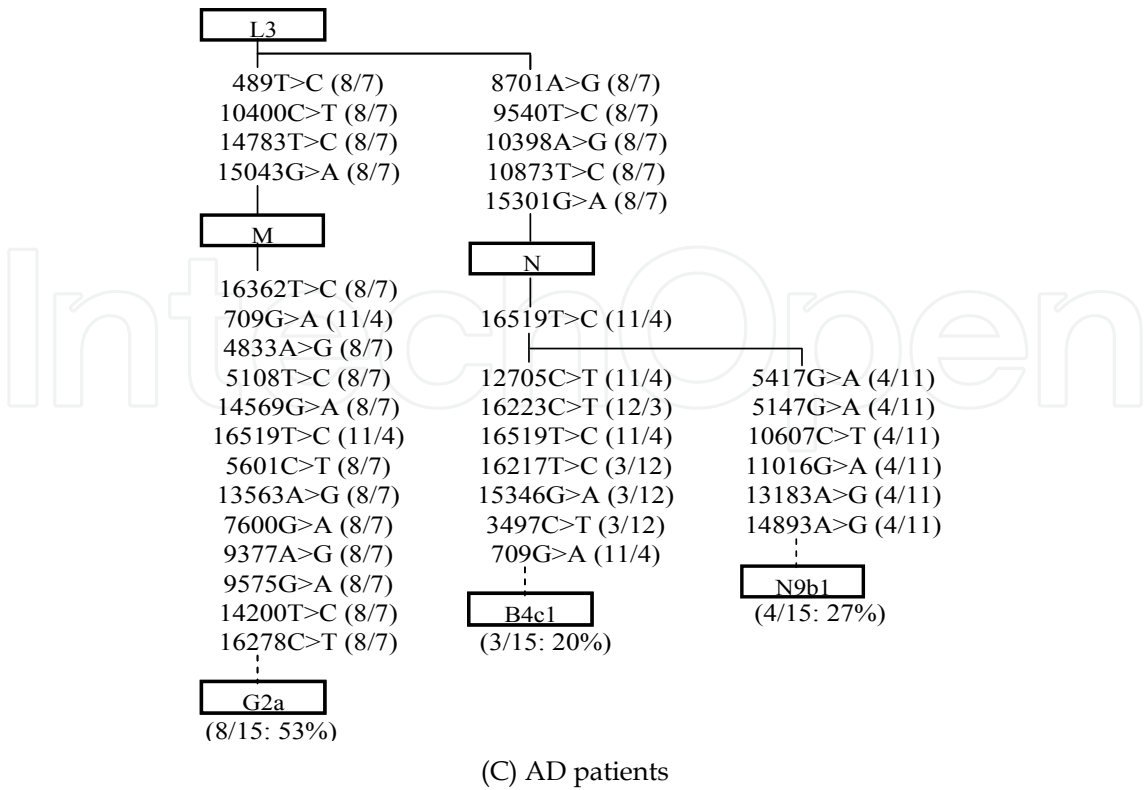
When the mtSNPs of the PD patients were classified by the RBF-based method described above, ten mtSNP clusters were obtained. The average predicted probabilities of these clusters for becoming the PD patients were respectively 63%, 62.5%, 52.9%, 30%, 29.4%, 15.4%, 7.7%, 4.3%, 3.4% and 0%. Then the 15 individuals with the highest probabilities of becoming PD patients were selected using the modified classification method, and their nucleotide distributions at individual mtDNA positions were examined. After that, the relations between Asian/Japanese haplogroups and the mtSNPs for the PD patients were examined (Herrnstadt *et al.* 2002; Kong *et al.* 2003; Tanaka *et al.* 2004). The associations between the haplogroups and mtSNPs for the PD patients are shown in Fig. 2. The features of associations for the PD patients were L3-M-M7b2 (33%), L3-M-G2a (27%), L3-N-B4e (13%), B5b (13%), and N9a (7%).

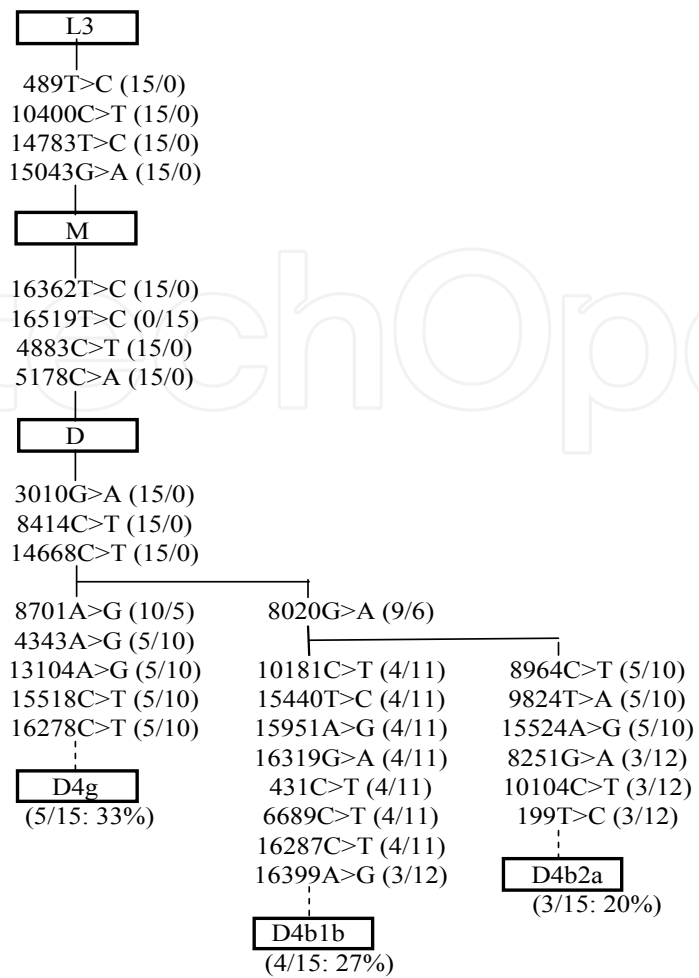


(A) PD patients



(B) Centenarians





(E) Non-obese young males

Fig. 2. Associations between haplogroups and the mtSNPs of the 15 persons with the highest probabilities of becoming PD patients. This description of associations is based on the phylogenetic tree for macrohaplogroups M and N described in Tanaka *et al.* [26]. The locus of mtDNA polymorphism (*mmm*), the normal nucleotide (rCRS) at the position *mmm* (N_N), the mtDNA mutation at that position (N_M), the number of the mtDNA mutations at *mmm* in individual clusters (Y), and the number of the normal nucleotides at *mmm* in individual clusters (X) are expressed as $mmmN_N>N_M(Y/X)$. For example, 489T>C (10/5) indicates the mtDNA locus (489), the normal nucleotide at that position (T), the mutation at that position (C), the number of mutations (10), and the number of the normal nucleotides in the cluster (5). (B) Centenarians, (C) AD patients, (D) T2D patients, (E) Non-obese young males.

To compare the mitochondrial haplogroups of the PD patients with those of other classes of people, we used the same modified method to examine the relations between the other four classes (i.e., centenarians, AD patients, T2D patients, and non-obese young males) and their mtSNPs. The associations between the haplogroups and mtSNPs for four classes of Japanese people are shown in Fig. 2 B to E. The centenarians were associated haplogroups L3-M-M7b2 (40%), L3-M-D-D4b2a (27%), and L3-N-B5b (20%); the AD patients were associated haplogroups L3-M-G2a (53%), L3-N-B4c1 (20%), and N9b1 (27%); the T2D patients were associated haplogroups L3-M-D-D4 (13%), L3-M-M8a1 (13%), G (13%), L3-N-B5b (20%), and F1 (13%); and the healthy non-obese young males were associated haplogroups L3-M-D-D4g

(33%), D4b2a (20%), and D4b1b (27%). The relations among the haplogroups for these five classes of people are listed in Table 1.

Classification consideration	PD patients	Centenarians	AD patients	T2D patients	Non-obese males
15 persons from the top				M8a1 (13%)	
	M7b2 (33%)	M7b2 (40%)		G (13%)	
	G2a (27%)		G2a (53%)		
				D4 (13%)	
					D4b1b (27%)
					D4b2a (20%)
		D4b2a (27%)			
					D4g (33%)
	B4e (13%)				
	B5b (13%)	B5b (20%)		B5b (20%)	
			B4c1 (20%)		
	N9a (7%)				
Persons whose probabilities are greater than 50%					
				F1 (13%)	
				M8a1 (4%)	
	M7a1a (19%)				
	M7b2 (14%)	M7b2 (13%)			
				G (11%)	
			G1 (9%)		
	G1a (14%)				
	G2a (11%)		G2a (17%)		
			D4 (19%)	D4 (47%)	
		D4a (15%)			
					D4b1b (24%)
					D4b2 (35%)
		D4b2a (9%)			
		D4b2b (16%)			
					D4g (29%)
				D5a (6%)	
	B4e (5%)				
			B4c1 (11%)		
	B5b (5%)	B5b (7%)		B5b (6%)	
	N9a (16%)		N9a (4%)		
			N9b1 (9%)	N9b1 (6%)	
			F1 (11%)	F1 (6%)	

Table 1. The relations among the haplogroups for five classes of people

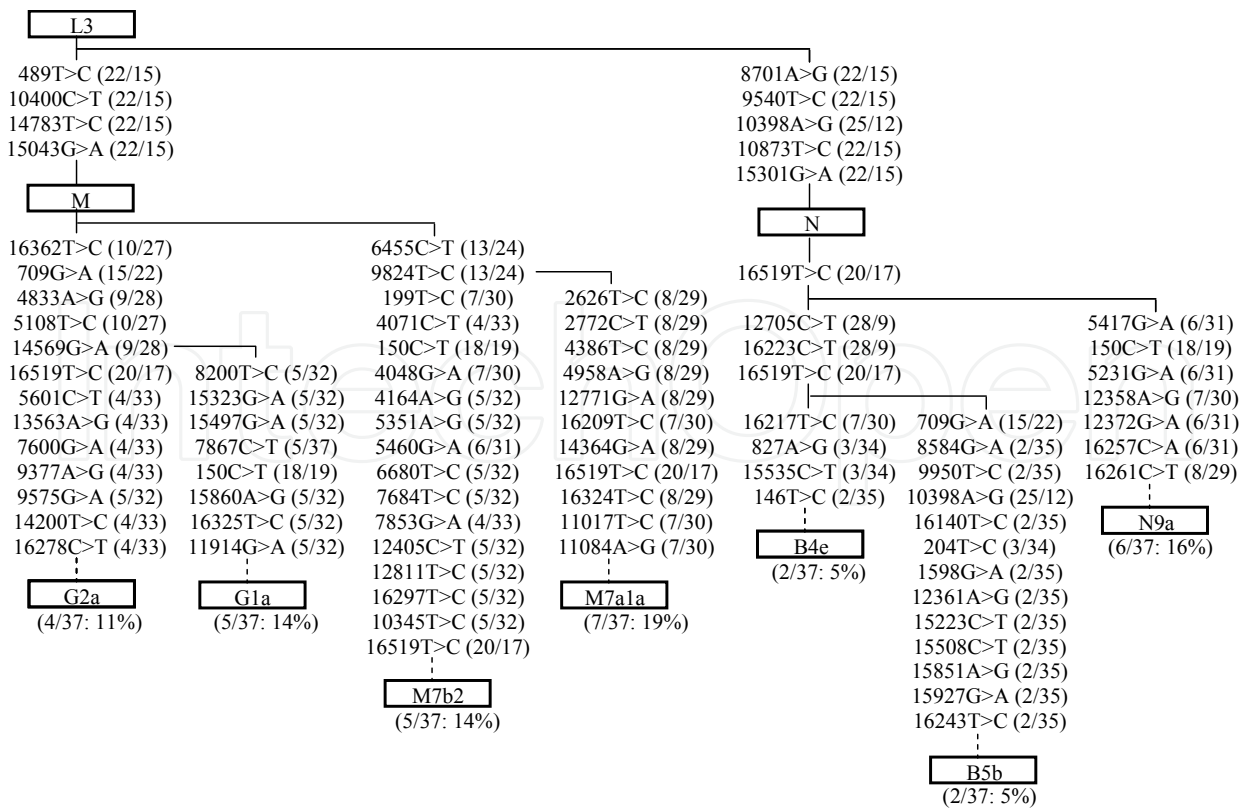
In Table 1 we see that the haplogroup Mb2 was common in PD patients and centenarians, G2a was common in PD patients and AD patients; and B5b was common in PD patients, centenarians, and T2D patients. The haplogroups of the PD patients are therefore different from those of the other four classes of people. The results are therefore considered new findings.

Then individuals whose probabilities of becoming PD patients were greater than 50% were selected, and the nucleotide distributions of those 37 persons were examined. The associations between haplogroups and the mtSNPs of those PD patients are shown in Fig. 3. Individuals whose probabilities of becoming PD patients were greater than 50% were classified into more haplogroups than were the 15 persons most likely to become PD patients. The ratios of the haplogroups M7b2, G2a, B4e, B5b and N9a for the 15 persons most likely to become PD patients were respectively changed from 33% to 14%, 27% to 11%, 13%

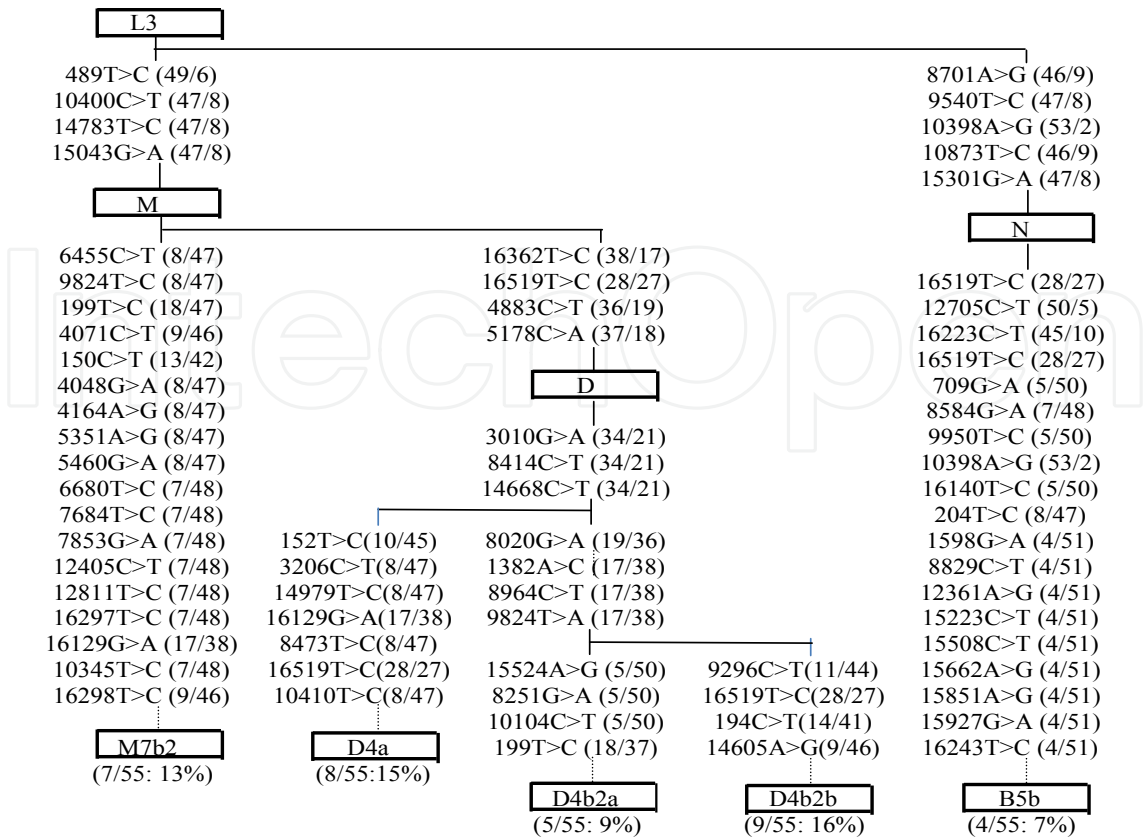
to 5%, 13% to 5%, and 7% to 16%, and new haplogroups M7a1a (19%) and G1a (14%) were classified for the persons whose probabilities were greater than 50%. The other four classes of people were also examined for the persons whose probabilities were greater than 50%. The selected numbers of the four classes were 55 for centenarians, 47 for AD patients, 47 for T2D patients, and 17 for healthy non-obese young males. The associations between the haplogroups and mtSNPs for four classes of people are shown in Fig. 3 B to E. The centenarians were associated haplogroups L3-M-M7b2 (13%), L3-M-D-D4a (15%), D4b2a (9%), D4b2b (16%), and L3-N-B5b (7%); the AD patients were associated haplogroups L3-M-G1 (9%), G2a (17%), L3-M-D-D4 (19%), L3-N-F1 (11%), B4c1 (11%), N9a (4%), and N9b1 (9%); the T2D patients were associated haplogroups L3-M-M8a1 (4%), G (11%), L3-M-D-D4 (47%), D5a (6%), L3-N-F1 (6%), B5b (6%), and N9b1 (6%); and the healthy non-obese young males were associated haplogorups L3-M-D-D4g (29%), D4b1b (24%), and D4b2 (35%). The relations among the haplogroups of the selected persons for the five classes of people are also listed in Table 1, where one sees that the individual classes of people were classified into more haplogroups when the mtSNP analysis was based on the persons whose probabilities were greater than 50% than they were when the analysis was based on the highest 15 persons from the top.

3.2 Comparison with previous works for T2D patients and Centenarians

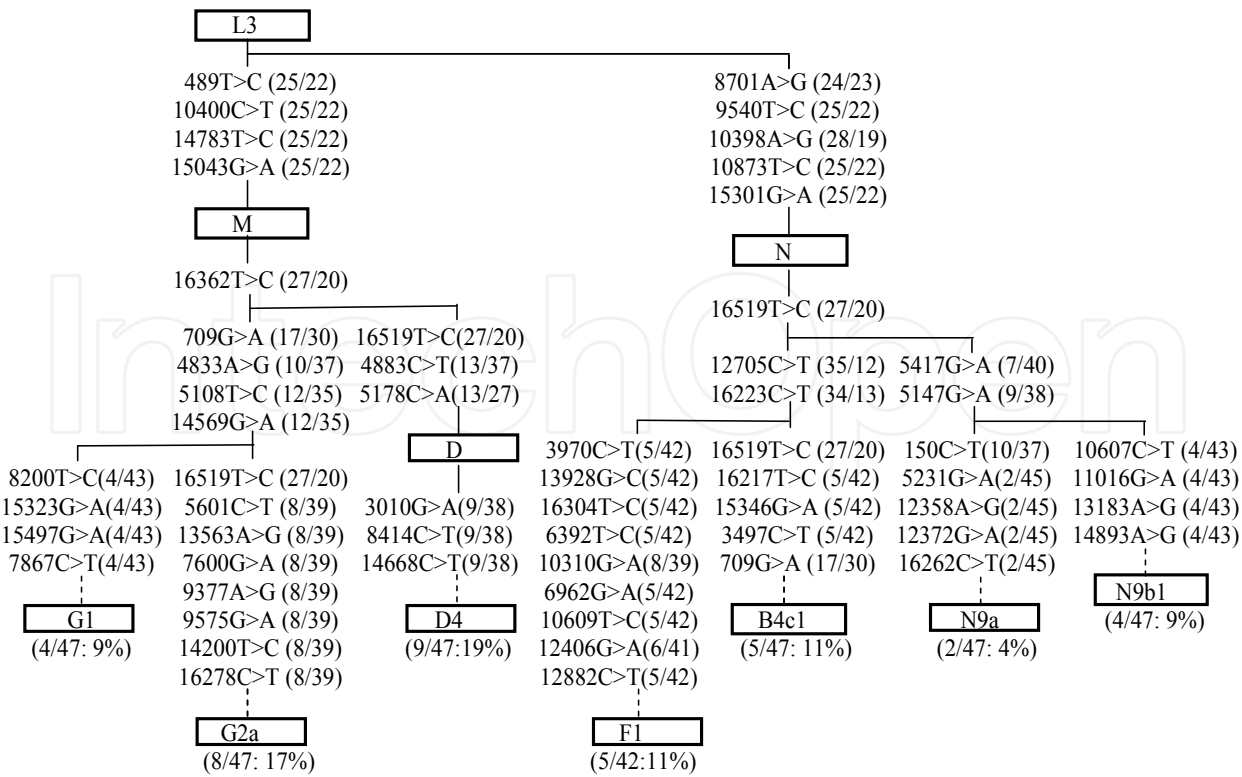
Although there is no report regarding the relations between mtSNP haplogroups and PD patients but there were a few studies concerning the relations between mtSNP haplogroups and T2D patients or centenarians, the differences between previous works and the work reported here are discussed based on the mtSNP haplogroups obtained.



(A) PD patients



(B) Centenarians



(C) AD patients

Fuku et al. (2007) reported that the mitochondrial haplogroup F in Japanese individuals had a significantly increased risk of type 2 diabetes mellitus (T2DM) (odds ratio 1.53, $P=0.0032$) using hospital based sampling data for large-scale association study (Fuku et al., 2007). They indicated that there were three mtSNPs in the haplogroup F – 3970C>T, 13928G>C, and 10310G>A. In the present analysis, the risk of T2D patients for the haplogroup F1 was approximately 13% (Fig. 2D). Other haplogroups related to the risk of T2D patients were B5b (20%), M8a1 (13%), D4 (13%) and G (13%) (Fig. 2D and Table 2). There were therefore big differences between the analyses of Fuku et al. (2007) and the results reported here. The significantly increased risk of T2DM was the haplogroup F in Fuku et al. (2007), whereas that of the results obtained was the haplogroup B5b. Although Fuku et al. (2007) indicated that the haplogroup F was the increased risk of T2DM, the F has four sub-haplogroups F1, F2, F3, and F4. In the work reported here, the only haplogroup F1 was obtained by the modified clustering method. The haplogroup F by Fuku et al. (2007) was characterized by three mtSNPs—3970C>T, 13928G>C, and 10310G>A, whereas the haplogroup F1 by the proposed method was featured by many mtSNPs—3970C>T, 13928G>C, 16304T>C, 6392T>C, 10310G>A, 6962G>A, 10609T>C, 12406G>A, and 12882C>T (Tanaka et al., 2004) (Fig. 2D). Furthermore, as Saxena et al. (2006) reported that there was no evidence of association between common mtDNA polymorphism and type 2 diabetes mellitus, the results obtained may indicate new findings for T2D patients (Saxena et al., 2006).

In addition, Alexe et al. (2007) reported the associations between Asian haplogroups and the longevity of Japanese people using the same GiiB data (Alexe et al., 2007). They showed the enrichment of longevity phenotype in mtDNA haplogroups D4b2b, D4a, and D5 in the Japanese population using statistical techniques (*t*-test and *P*-value). However, the results here showed that the haplogroups M7b2, D4b2a, and B5b were associated with Japanese centenarians. There is therefore no common haplogroup in both methods. Alexe et al. (2007) showed that the haplogroup D5 was characterized by mtSNPs 11944T>C, 12026A>G, 1107T>C, 5301A>G, 10397A>G, and 752C>T, whereas there was no frequency in the corresponding mtSNPs in the present analysis. Although they reported that the centenarian enrichment was not found in the haplogroup D4b2a, the present results showed that the corresponding D4b2a was characterized by many mtSNPs with a frequency of 27% (Fig. 2B). Although Alexe et al. (2007) described that there was no haplogroup having mtSNPs significantly enriched in centenarians other than D mega-group in M macrohaplogroup, the present analysis indicated that the haplogroup M7b2 was characterized by many mtSNPs (Fig. 2B and 3B). They also reported that there was no enrichment haplogroup for centenarians in macrohaplogroup N, whereas the haplogroup B5b obtained by the proposed method also had many mtSNPs enriched in centenarians (Figs. 2B and 3B).

Bilal et al. (2008) reported the haplogroup D4a was a marker for extreme longevity in Japan by analyzing the complete mtDNA sequences from 112 Japanese semi-supercentenarians (aged over 105 years old) combined with previously published data (Bilal et al., 2008). These semi-supercentenarians were also examined using the proposed method. Since the predicted probabilities of individual clusters for the semi-supercentenarians were lower than those of the centenarians, 43 individuals with predicted probabilities over 46% (the average is 54%) were selected. The obtained results were the haplogroups D4a (30%), B4c1a (14%), M7b2 (12%), F1 (9%), M1 (7%) and B5b (2%) shown in Fig. 4. As the highest haplogroup was D4a, this was the same as the marker described by Bilal et al. (2008). However, there are other haplogroups indicating the characteristics of semi-

supercentenarians. This means that other haplogroups also have the possibilities of becoming semi-supercentenarians. The common haplogroups between the centenarians and semi-supercentenarians were M7b2 and B5b.

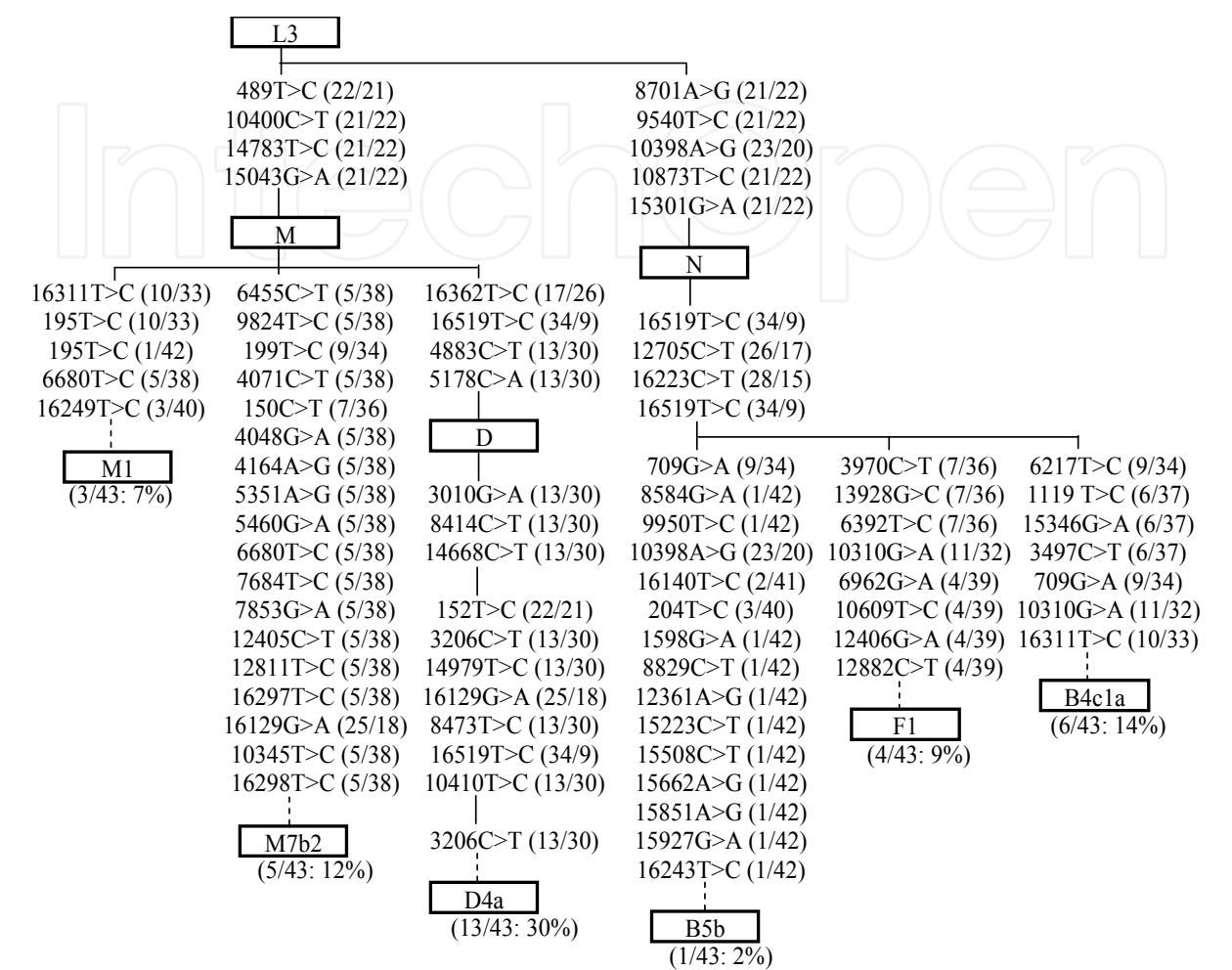


Fig. 4. Associations between Asian/Japanese haplogroups and mtSNPs of semi-supercentenarians.

3.3 Differences between statistical technique and the modified RBF method

Although the haplogroups of the PD patients were obtained by the modified RBF method, there are clear differences between the previously reported statistical technique and the method described here. As the previously reported methods analyzed the relations between mtSNPs and Japanese PD patients, centenarians, AD patients, T2D patients, or semi-supercentenarians using standard statistical techniques (Alexe et al., 2007; Fuku et al., 2007; Bilal et al., 2008), they could not indicate mutual relations among the other classes of people—centenarians, AD patients, T2D patients and healthy non-obese young males. On the other hand, the proposed method was able to show differences and mutual relations among these classes of people. In addition, the prediction probabilities of associations between mtSNPs and these classes of people cannot be obtained by the statistical techniques used in the previous methods, whereas the method proposed is able to compute them based on learning mtSNPs of individual classes.

It is considered that the relations among individual mtSNPs for these classes of people should be analyzed as mutual mtSNP connections in the entire mtSNPs. A learning method, a RBF network, was therefore adopted for extracting individual characteristics from the entire mtSNPs, although the previous methods used standard statistical techniques.

	Statistical technique	Proposed method
Technique	Relative relations between target and normal data	Supervised learning (RBF) by using correct and incorrect data
Analysis position	Each locus of mtDNA polymorphisms (independent position)	Entire loci of mtDNA polymorphisms (successive positions)
Input (required data)	Target (individual cases) and control (normal data)	Correct (individual cases) and incorrect (others except correct)
Output (results)	Odds ratio or relative risk	Clusters with predictions
Analysis	Check odds ratio or relative risk at each position	Check individuals in clusters based on prediction probabilities

Table 2. Differences between the statistical technique and the proposed (modified RBF) method

The differences between standard statistical technique and the proposed method are listed in Table 2. In the statistical technique, the analysis of odds ratios or relative risks is based on the relative relations between target and control data at each polymorphic mtDNA locus. In the modified RBF method, on the other hand, clusters indicating predicted probabilities are examined on the basis of the RBF using correct and incorrect data for the entire polymorphic mtDNA loci. The statistical technique determines characteristics of haplogroups using independent mtDNA polymorphisms that indicate high odds ratios, whereas the modified RBF method determines them by checking individuals with high predicted probabilities. This means that the statistical technique uses the results of independent mutation positions, whereas the modified RBF method uses the results of entire mutation positions. As there are the differences between the two methods, which method is better depends on future research. Furthermore, the method described here may have possibilities for use in the initial diagnosis of various diseases or longevity on the basis of the individual predicted probabilities.

4. Acknowledgement

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Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. The main obstacle to developing neuroprotective therapies is a limited understanding of the key molecular mechanisms that provoke neurodegeneration. The discovery of PD genes has led to the hypothesis that misfolding of proteins and dysfunction of the ubiquitin-proteasome pathway are pivotal to PD pathogenesis. Previously implicated culprits in PD neurodegeneration, mitochondrial dysfunction, and oxidative stress may also act in part by causing the accumulation of misfolded proteins, in addition to producing other deleterious events in dopaminergic neurons. Neurotoxin-based models have been important in elucidating the molecular cascade of cell death in dopaminergic neurons. PD models based on the manipulation of PD genes should prove valuable in elucidating important aspects of the disease, such as selective vulnerability of substantia nigra dopaminergic neurons to the degenerative process.

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