HHS Public Access

Author manuscript

Neurosci Lett. Author manuscript; available in PMC 2016 July 06.

Published in final edited form as:

Neurosci Lett. 2015 February 5; 587: 98–101. doi:10.1016/j.neulet.2014.12.005.

Association of the mt-ND2 5178A/C polymorphism with Parkinson's disease

Aaron M. Gusdon[a,b,c,1], **Fang Fang**[a,1], **Jing Chen**[d], **Clayton E. Mathews**[d], **Wang Li**[e], **Charleen T. Chu**[b], **Jian-Qing Ding**[a], and **Sheng-di Chen**[a,*]

[a]Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, No. 197, Rui Jin Er Road, Shanghai 200025, China

[b]Department of Pathology, Division of Neuropathology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA

[c]Department of Neurology, Weill Cornell Medical College, New York, NY 10065, USA

[d]Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL 32610-0275, USA

[e]Clinical and Translational Science Institute (CTSI), University of Pittsburgh School of Medicine, Pittsburgh, PA15261, USA

Abstract

Mitochondria play an important role in the etiology of Parkinson's disease (PD). While mutations in the mitochondrial DNA (mtDNA) have been shown to accumulate in PD, no specific mtDNA polymorphisms have been associated with susceptibility or resistance to PD. A cytosine to adenine transversion at base pair 5178 in the mtDNA has been associated with increased longevity and resistance against a number of age related disorders and has been shown to decrease mitochondrial reactive oxygen species (ROS) production. We sought to determine whether 5178A is associated with resistance against PD in a Han Chinese population. To assesses its association with PD, we genotyped 484 idiopathic PD patients and 710 control individuals for 5178C/A. Genotyping was performed using restriction fragment length polymorphism (RFLP) analysis. There was no significant association between 5178A and PD ($P = 0.308$) when analyzing the entire population. However, sub-group analysis revealed that in males the frequency of 5178A was significantly lower in PD patients (27.7% in controls vs 20.0% in PD patients, $P = 0.027$). Stratification of the population by age showed that this trend held across age groups but only reached statistical significance in males aged 60–70 (29.1% in controls vs 14.05 in PD patients, $P = 0.011$). In conclusion, we demonstrated that the frequency of 5178A was significantly decreased in male PD patients in a Han Chinese population. This polymorphism may be associated with resistance against the development of PD when in combination with loci on the Y chromosome.

*Corresponding author. Tel.: +1 7247666161. chensd2001@hotmail.com (S.-d. Chen).

[1]These authors contributed equally.

Conflict of interest

The authors declare no conflict of interest.

Keywords

Parkinson's disease; Mitochondrial DNA; 5178A; mt-ND2; NADH dehydrogenase; Complex I

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease typically characterized by bradykinesia, rigidity, and resting tremor. The incidence of PD has been estimate at 1% by 65 years of age and 4–5% by 85 years of age [1,2]. Cases of post-encephalitic and toxin mediated PD laid the foundation for the belief throughout most of the 20th century that PD was primarily arose due to environmental factors [3–5]. However, over the past two decades, mutations in several genes have been shown to cause PD [1,2]. While less than 10% of PD is thought to arise from monogenic mutations [1], interactions between polymorphisms in a variety of other genes in combination with environmental factors likely contributes to a higher percentage of otherwise idiopathic PD cases.

A central theme among the genes found to be associated with PD to date has been their effect on mitochondria. Alpha-synuclein accumulation contributes to mitochondrial fragmentations and also impairs function of NADH:ubiquinone oxidoreductase (complex I) [6]. PINK1 and PARKIN participate in the turnover of mitochondria through mitophagy, and mutations in either gene can result in accumulation of dysfunctional mitochondria [7,8]. DJ-1 plays a role in attenuating oxidative stress, and loss of function mutations contribute to susceptibility of dopaminergic neurons to cell death [9,10]. Mutations in LRRK2 impair calcium handling and subsequently mitochondrial turnover and also likely play a role in susceptibility to oxidative stress and complex I dysfunction. Additionally, toxins causing PD such as rotenone and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), are known to inhibit complex I [11,12].

Even before the impact of these genes on mitochondrial function was known, impaired mitochondrial complex I activity in the substantia nigra and accumulations of mitochondrial DNA (mtDNA) mutations had been demonstrated in PD [13]. However, to date, no consistent association has been demonstrated between mutations in the mtDNA and PD [14]. Previously, a cytosine to adenine transversion at position 5178 in the mtDNA, which results in a leucine to methionine amino acid substitution in the second subunit of complex I (mt-ND2) has been associated with increased longevity [15] as well as resistance against a number of other conditions such as hypertension [16], atherosclerosis [17], dyslipidemia [18], type 1 diabetes [19], and pulmonary function [20]. Recently the D4a haplogroup has also been suggested to reduce the risk of ischemic stroke in a Chinese population [21]. Oxidative stress and increased reactive oxygen species (ROS) production has been implicated in the pathogenesis of many of these disorders, and it was proposed that 5178A may reduce oxidative stress on the basis of the additional methionine residue added to complex I [20,22]. Experimental evidence has not supported a role for 5178A in resistance to ROS, however the adenine encoding allele was shown to decrease endogenous ROS production from complex I [23]. Further, in an mouse model of type 1 diabetes, 5178A increased resistance of beta cells against autoimmune destruction [24].

Given the importance of ROS and oxidative stress in PD and the association of the 5178A polymorphism with resistance against other age related disorders, we hypothesized that 5178A would be associated with a decreased frequency of PD. Importantly, 5178A defines mitochondrial haplogroup D and is not commonly found in Western populations [25]. We therefore genotyped Han Chinese individuals with or without PD and assessed the frequency of 5178A.

2. Methods

Study population: a total of 484 Han Chinese patients with PD were recruited from the Shanghai area. All patients were diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [26], and had at least 2 of 3 of the major clinical criteria defined as bradykinesia, tremor, and rigidity. Each patient was diagnosed in the neurology clinic at Ruijin Hospital. Patients with a positive family history of PD were excluded. A total of 710 control subjects were included. Each of the control subjects had no evidence of neurodegenerative disease. All of the subjects included in this study came from the same Han Chinese ethnic background and resided in the Shanghai area. Patient data are detailed in Table 1.

Genotyping

DNA was extracted form blood leukocytes using standard methods. Restriction fragment length polymorphism analysis was use to distinguish between 5178C and 5178A within the mtDNA as described [18]. The primers used for polymerase chain reaction (PCR) amplification were as follows: forward 5′-CTTAGCATACTCCTCAATTACCC-3′ and reverse 5′-CTGAATTCTTCGATAATGGCCCA-3′. Following an initial denaturation at 94 °C, 40 PCR cycles were performed as follows: denaturation at 94 °C for 30 s, annealing at 60 °C for 60 s, and extension at 72 °C for 90 s. Following the 40 cycles, a final extension step at 72 °C for 10 min. After PCR amplification, the product was digested with the restriction enzyme *Alu*I (New England Biolabs, Beijing, China). Electrophoresis was then performed in a 1.5% agarose gel containing ethidium bromide and visualized with UV light. The presence of the *Alu*I cut site was designated as 5178C while the absence of this site was designated as 5178A.

Statistical analysis

descriptive statistics were reported using mean ± SD for age and frequencies with percentages for gender, HTN, genotype between controls and PD patients. Univariate analysis was conducted using Chi-Square test for the categorical variables and independent-sample *t*-test for the continuous variables. Subgroup analysis was performed to examine the association between genotype with the outcome of PD within stratified gender and age groups. A P value < 0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences 21 (SPSS, Chicago, IL, USA).

3. Results

Characteristics of the control subject and PD patients are shown in Table 1. Univariate analysis demonstrated that age and gender were significant confounders between the control and PD groups. There were significantly more females in the control group and males in the PD group. Age was significantly lower in the PD group. The percentage of patients with hypertension was not significantly different between the groups. Information regarding type 2 diabetes was only available for patients in the control group. Among the individuals in the control group encoding 5178C, 468 (86.5%) did not have diabetes and 73 (13.5%) did. Among those encoding 5178A, 144 (85.25) did not have diabetes and 25 (14.8%) did. There was no significant difference in the percentage of individuals with diabetes comparing those encoding 5178C and 5178A ($P = 0.669$).

Multivariate regression logistic regression analysis with adjustment for age, gender, and hypertension revealed that the frequency of 5178A was not significantly between the control and PD groups when including both genders and all ages (Table 2). Sub-group analysis assessing each gender individually showed that the frequency of 5178A was significantly lower in the PD group in males but not in females. When stratifying by age, the frequency of 5178A was not significantly different between the control and PD groups across all age groups when combining both genders or considering females alone. There was a trend toward decreased frequency of 5178A in the PD group in males among all age groups analyzed, however it only reached statistical significance in the 60–70 year old group.

4. Discussion

Mitochondrial dysfunction has clearly been implicated in the pathogenesis of genetic and toxin models of PD. However specific mtDNA polymorphisms have not been consistently associated with PD. Herein, we demonstrated that while the frequency of 5178A was not lower in our total PD population, the frequency of this allele was significantly lower in males with PD compared with the corresponding control subjects. This difference remained significant in the 60–70 year old age group. While the trend remained in the less than 60, greater than 60, and greater than 70 age groups, it failed to reach statistical significance. The lack of statistical significance in these age groups was likely a result of a relatively low sample size in these sub-groups.

The finding that the frequency of 5178A only showed a significant difference in males is perhaps not entirely unexpected. It is well known that mitochondrial genes can interact with various nuclear loci [27–29]. Indeed, a previous study has suggested that the adenine containing allele of mt-ND2 interacts with as of yet undefined nuclear loci [30], including interactions with the Y Chromosome [31]. Additionally, one previous study demonstrated that the effects of 5178A differed between males and females with regard to hypertension [16]. It is therefore conceivable that loci within the Y chromosome modify the effects of 5178A in the context of PD. Linkage analysis studies would be necessary to demonstrate which loci on the Y chromosome interact with 5178A. Furthermore, studies in mice would be particularly useful in determining whether the effects of 5178A on lowering mitochondrial ROS production vary in the presence or absence of a Y chromosome.

These results demonstrating a gender specific effect of 5178A may help to explain the discrepancies in some previous studies. While 5178A was shown to be associated with increased longevity in a Japanese population [15] as well as a Uygur population [32], no significant difference was found in a Han Chinese population [33]. The latter study which failed to demonstrate significance did not perform subgroup analysis based on gender, and for this reason may not found a significant association in their cohort. However, these results must be considered in the context of the mtDNA diversity of the Chinese population. Indeed, the incidence of 5178A and thus mitochondrial haplogroup D has been shown to increase from Southern to Northern China [25]. As expected the study participants utilized here exhibited a higher frequency of 5178A in both the control and PD populations when compared to the study from Yao et al. that included individuals from Yunan in the southwest of China [33]. However, the allele frequency of 5178A in our population did not reach the frequencies reported in Japan [17,18,20,34] The increased frequency of 5178A in Japanese populations makes sense when considering that most migration to Japan came from Northern Asian populations, with some notable exceptions [35].

Mitochondrial haplogroups have been suggested to impart physiological benefit in the context of the environment in which they evolved [36–38]. Given the increase prevalence of haplogroup D among northern populations including the Siberian Inuits [39], it has been proposed that 5178A may confer increased metabolic flexibility in adaptation to cold climates or seasonal variations [40]. Of interest, the effect of polymorphisms on mitochondrial function has been shown to be modulated by the haplogroups with which they are associated [41]. Therefore, as 5178A may play a role in climate adaptation, it may also modulate of pathogenicity of other polymorphisms known to be associated with PD. It may thus be of interest to examine whether the pathological effects of genes such as *SNCA, LRRK2, PINK1, PARK2*, and *ATP13A2* are modulated in the context of 5178A.

In conclusion, our results demonstrate that the frequency of 5178A is significantly lower in male PD patients. However, these data raise numerous additional questions. Experiments should be performed to verify the association of 5178A with PD in populations from other regions. Furthermore, the mechanisms of the potentially cytoprotective effects of 5178A need to be confirmed within neurons in models of PD.

Acknowledgments

The project described was supported by the National Institutes of Health through Grants UL1TR000005, R01DK074656, and 5R01AG026389-07.

References

1. Trinh J, Farrer M. Advances in the genetics of Parkinson disease. Nat Rev Neurol. 2013; 9:445–454. http://dx.doi.org/10.1038/nrneurol.2013.132. [PubMed: 23857047]
2. Farrer MJ. Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet. 2006; 7:306–318. http://dx.doi.org/10.1038/nrg1831. [PubMed: 16543934]
3. Hunt EL, Cornwall LH. The postencephalopathic Parkinson syndrome. JAMA. 2014; 311
4. Bove J, Prou D, Perier C, Przedborski S. Toxin-induced models of Parkinson's disease. J Am Soc Exp Neurother. 2005; 2:484–494.

5. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983; 219:979–980. [PubMed: 6823561]
6. Nakamura K. α-Synuclein and mitochondria: partners in crime? Neurotherapeutics. 2013; 10:391–399. http://dx.doi.org/10.1007/s13311-013-0182-9. [PubMed: 23512373]
7. Chu CT. A pivotal role for PINK1 and autophagy in mitochondrial quality control: implications for Parkinson disease. Hum Mol Genet. 2010; 19:R28–37. http://dx.doi.org/10.1093/hmg/ddq143. [PubMed: 20385539]
8. Zhu J, Wang KZQ, Chu CT. After the banquet: mitochondrial biogenesis, mitophagy, and cell survival. Autophagy. 2013; 9:1663–1676. [PubMed: 23787782]
9. Mccoy MK, Cookson MR. DJ-1 regulation of mitochondrial function and autophagy through oxidative stress. Autophagy. 2011; 7:531–532. http://dx.doi.org/10.1093/hmg/ddq430.he. [PubMed: 21317550]
10. Guzman JN, Sanchez-Padilla J, Wokosin D, Kondapalli J, Ilijic E, Schumacker PT, et al. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature. 2010; 468:696–700. http://dx.doi.org/10.1038/nature09536. [PubMed: 21068725]
11. Greenamyre JT, Sherer TB, Betarbet R, Panov AV. Complex I and Parkinson's disease. IUBMB Life. 2001; 52:135–141. http://dx.doi.org/10.1080/15216540152845939. [PubMed: 11798025]
12. Sanders LH, Greenamyre JT. Oxidative damage to macromolecules in human Parkinson disease and the rotenone model. Free Radical Biol Med. 2013; 62:111–120. http://dx.doi.org/10.1016/j.freeradbiomed.2013.01.003. [PubMed: 23328732]
13. Mann VM, Coopepb JM, Schapira AHV. Quantitation of a mitochondrial DNA deletion in Parkinson's disease. FEBS. 1992; 299:218–222.
14. Simon DK, Pankratz N, Kissell DK, Pauciulo MW, Halter CA, Rudolph A, et al. Maternal inheritance and mitochondrial DNA variants in familial Parkinson's disease. BMC Med Genet. 2010; 11:53. http://dx.doi.org/10.1186/1471-2350-11-53. [PubMed: 20356410]
15. Tanaka M, Gong J, Zhang J, Yoneda M. Mitochondrial genotype associated with longevity. Lancet. 1998; 351:185–186. [PubMed: 9449878]
16. Kokaze A, Ishikawa M, Matsunaga N, Yoshida M, Sekine Y, Sekiguchi K, et al. Longevity-associated mitochondrial DNA 5178A/C polymorphism and blood pressure in the Japanese population. J Hum Hypertens. 2004; 18:41–45. http://dx.doi.org/10.1038/sj.jhh.1001632. [PubMed: 14688809]
17. Hajime Matsunaga RK, Tanaka Y, Tanaka M, Gong J-S, Zhang J, Nomiyama T, Ogawa O, Ogihara T, Yamada Y, Yagi K. Antiatherogenic mitochondrial genotype in patients with type 2 diabetes. Diabetes Care. 2001; 24:500–503. [PubMed: 11289475]
18. Kokaze A, Ishikawa M, Matsunaga N, Yoshida M, Sekine Y, Teruya K, et al. Association of the mitochondrial DNA 5178 A/C polymorphism with serum lipid levels in the Japanese population. Hum Genet. 2001; 109:521–525. http://dx.doi.org/10.1007/s004390100602. [PubMed: 11735027]
19. Yasuko Uchigata MT, Okada T, Gong J-S, Yamada Y, Iwamoto Y. A mitochondrial genotype associated with the development of autoimmune-related type 1 diabetes. Diabetes Care. 2002; 25:2106. [PubMed: 12401767]
20. Kokaze A, Ishikawa M, Matsunaga N, Yoshida M, Satoh M, Teruya K, et al. Longevity-associated mitochondrial DNA 5178C/A polymorphism and its interaction with cigarette consumption are associated with pulmonary function in middle-aged Japanese men. J Hum Genet. 2007; 52:680–685. http://dx.doi.org/10.1007/s10038-007-0171-0. [PubMed: 17636359]
21. Yang, D.; Wang, Q.; Shi Fan, YY.; Zheng, H-X.; Song, G., et al. Mitochondrial DNA haplogroup D4b is a protective factor for ischemic stroke in Chinese Han population; Mol Genet Genomics. 2014. p. 1-6.http://dx.doi.org/10.1007/s00438-014-0884-7
22. Kim G, Weiss SJ, Levine RL. Methionine oxidation and reduction in proteins. Biochim Biophys Acta. 2014; 1840:901–905. http://dx.doi.org/10.1016/j.bbagen.2013.04.038. [PubMed: 23648414]
23. Gusdon AM, Votyakova TV, Mathews CE. mt-Nd2a suppresses reactive oxygen species production by mitochondrial complexes I and III. J Biol Chem. 2008; 283:10690–10697. http://dx.doi.org/10.1074/jbc.M708801200. [PubMed: 18281288]

24. Chen J, Gusdon AM, Piganelli J, Leiter EH, Mathews CE. Mt-nd2 a modifies resistance against autoimmune type 1 diabetes in nod mice at the level of the pancreatic beta-cell. Diabetes. 2011; 60:355–359. http://dx.doi.org/10.2337/db10-1241. [PubMed: 20980458]
25. Yao YG, Kong QP, Bandelt HJ, Kivisild T, Zhang YP. Phylogeographic differentiation of mitochondrial DNA in Han Chinese. Am J Hum Genet. 2002; 70:635–651. http://dx.doi.org/10.1086/338999. [PubMed: 11836649]
26. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992; 55:181–184. http://dx.doi.org/10.1136/jnnp.55.3.181. [PubMed: 1564476]
27. Poyton R, Mcewen JE. Crosstalk between nuclear and mitochondrial genomes. Annu Rev Biochem. 1996; 65:563–607. [PubMed: 8811190]
28. Bar-Yaacov D, Blumberg A, Mishmar D. Mitochondrial-nuclear co-evolution and its effects on OXPHOS activity and regulation. Biochim Biophys Acta. 2012; 1819:1107–1111. http://dx.doi.org/10.1016/j.bbagrm.2011.10.008. [PubMed: 22044624]
29. Rodley CDM, Grand RS, Gehlen LR, Greyling G, Jones MB, O'sullivan JM. Mitochondrial-nuclear DNA interactions contribute to the regulation of nuclear transcript levels as part of the inter-organelle communication system. PLoS ONE. 2012; 7:e30943. http://dx.doi.org/10.1371/journal.pone.0030943. [PubMed: 22292080]
30. Gusdon AM, Votyakova TV, Reynolds IJ, Mathews CE. Nuclear and mitochondrial interaction involving mt-Nd2 leads to increased mitochondrial reactive oxygen species production. J Biol Chem. 2007; 282:5171–5179. http://dx.doi.org/10.1074/jbc.M609367200. [PubMed: 17189252]
31. Chen J, Lu Y, Lee C, Li R, Leiter EH, Clayton E. Commonalities of genetic resistance to spontaneous autoimmune and free radical-mediated diabetes. Free Radical Biol Med. 2008; 45:1263–1270. http://dx.doi.org/10.1016/j.freeradbiomed.2008.07.020. [PubMed: 18718526]
32. Nijiati M, Saidaming A, Qiao J, Cheng Z, Qiu C, Sun Y. GNB3, eNOS, and mitochondrial DNA polymorphisms correlate to natural longevity in a Xinjiang Uygur population. PLoS ONE. 2013; 8:e81806. http://dx.doi.org/10.1371/journal.pone.0081806. [PubMed: 24376503]
33. Yao YG, Kong QP, Zhang YP. Mitochondrial DNA 5178A polymorphism and longevity. Hum Genet. 2002; 111:462–463. http://dx.doi.org/10.1007/s00439-002-0826-z. [PubMed: 12384792]
34. Kokaze A, Ishikawa M, Matsunaga N, Yoshida M, Sekine Y, Teruya K, et al. Association of the longevity-associated mitochondrial DNA 5178A/C polymorphism with serum protein fraction levels in healthy Japanese women. Exp Gerontol. 2002; 37:931–936. http://dx.doi.org/10.1016/S0531-5565(02)32-3. [PubMed: 12086702]
35. Tanaka M, Cabrera VM, González AM, Larruga JM, Takeyasu T, Fuku N, et al. Mitochondrial genome variation in eastern Asia and the peopling of Japan. Genome Res. 2004; 14:1832–1850. http://dx.doi.org/10.1101/gr.2286304. [PubMed: 15466285]
36. Wallace DC, B PTRS. Bioenergetics in human evolution and disease: implications for the origins of biological complexity and the missing genetic variation of common diseases bioenergetics in human evolution and disease: implications for the origins of biological complexity. Philos Trans R Soc L B Biol Sci. 2013; 368:1–10.
37. Wallace DC. Mitochondria, bioenergetics, and the epigenome in eukaryotic and human evolution. Cold Spring Harbor Symp Quant Biol. 2009; 74:383–393. http://dx.doi.org/10.1101/sqb.2009.74.031. [PubMed: 19955254]
38. Wallace DC, Brown MD, Lott MT. Mitochondrial DNA variation in human evolution and disease. Gene. 1999; 238:211–230. http://www.ncbi.nlm.nih.gov/pubmed/10570998. [PubMed: 10570998]
39. Achilli A, Perego Ua, Bravi CM, Coble MD, Kong Q-P, Woodward SR, et al. The phylogeny of the four pan-American MtDNA haplogroups: implications for evolutionary and disease studies. PLoS ONE. 2008; 3:e1764. http://dx.doi.org/10.1371/journal.pone.0001764. [PubMed: 18335039]
40. Nishimura T, Motoi M, Niri Y, Hoshi Y, Kondo R, Watanuki S. Relationship between seasonal cold acclimatization and mtDNA haplogroup in Japanese. J Physiol Anthropol. 2012; 31:22. http://dx.doi.org/10.1186/1880-6805-31-22. [PubMed: 22929588]
41. Ji F, Sharpley MS, Derbeneva O, Alves LS, Qian P, Wang Y, et al. Mitochondrial DNA variant associated with Leber hereditary optic neuropathy and high-altitude Tibetans. Proc Natl Acad Sci U S A. 2012; 109:7391–7396. http://dx.doi.org/10.1073/pnas.1202484109. [PubMed: 22517755]

HIGHLIGHTS

- We investigated the association of the C5178A polymorphism with Parkinson's disease.
- A population of Han Chinese patients with Parkinson's disease was genotyped.
- Frequency of 5178A was significantly decreased in males with Parkinson's disease.
- 5178A may reduce the risk of Parkinson's disease in combination with nuclear loci.
- Mitochondria play a key role in the pathogenesis of Parkinson's disease.

Table 1

Patient characteristics are displayed for control and Parkinson's disease (PD) subjects. The gender distribution for each group is shown followed by the age distribution and age of onset for PD patients. The number of patients in each group with hypertension (HTN) is shown with the percentage of total for that group in parentheses.

General	Control	PD	*P* Value
Total	710	484	
Gender			
Male	332	266	0.005
Female	378	218	
Age	68.4 ± 10.6	60.6 ± 10.1	<0.001
Age at onset	NA	56.2 ± 10.2	
HTN	290(40.8)	185(38.2)	0.363

Table 2

Genotyping results are displayed for the 5178C/A polymorphism. The percentage of the designated group encoding 5178C or 5178A is displayed with the total number (*N*) below each percentage. The data for all age groups as well as subgroup analysis for each age group are displayed.

		All ages			Age <60 years			Age 60–70 years			Age >60 years			Age >70 years		
		Ctrl	**PD**	***P* value**	**Ctrl**	**PD**	***P* value**	**Ctrl**	**PD**	***P* value**	**Ctrl**	**PD**	***P* value**	**Ctrl**	**PD**	***P* value**
	5178C (%)	76.2	78.7	0.308	74.1	77.8	0.365	74.7	82.9	0.052	77.0	79.6	0.428	78.9	77.6	0.247
	N	541	381		152	186		168	136		389	195		221	59	
Total	5178A (%)	23.8	21.3		25.9	22.2		25.3	17.1		23.0	20.4		21.1	22.4	
	N	169	103		53	53		57	28		116	50		59	22	
	5178C (%)	79.6	77.1	0.461	79.0	77.9	0.910	77.9	78.9	0.870	80.0	76.2	0.407	81.9	70.6	0.139
	N	301	168		84	88		95	56		217	80		122	24	
Females	5178A (%)	20.4	22.9		21.0	22.1		22.1	21.1		20.0	23.8		18.1	24.0	
	N	77	50		23	25		27	15		54	25		27	10	
	5178C (%)	73.3	80.0	0.027	70.4	77.8	0.155	70.9	86.0	0.011	73.5	82.1	0.056	75.6	74.5	0.880
	N	240	213		68	98		73	80		172	115		99	35	
Males	5178A (%)	27.7	20.0		31.6	22.2		29.1	14.0		26.5	17.9		24.4	25.5	
	N	92	53		30	28		30	13		62	256		32	12	