

CYP2D6 gene polymorphism as a probable risk factor for Alzheimer's disease and Parkinson's disease with dementia

Polimorfizm genu CYP2D6 jako prawdopodobny czynnik ryzyka choroby Alzheimera i choroby Parkinsona przebiegającej z otępieniem

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Abstract

Background and purpose: The theory of multifactorial inheritance is considered in the pathogenesis of sporadic Alzheimer's disease (AD) and Parkinson's disease (PD); therefore, it makes the genes regulating bioactivation or detoxification of exogenous substances candidates of sensitivity to Alzheimer's and Parkinson's diseases. The aims of the study were: 1) to determine the genotypes of *CYP2D6* cytochrome (*CYP2D6*) in patients with AD and sporadic PD with dementia; 2) to evaluate the relationship between the *CYP2D6* genotype and the age of onset of the disease, the extent of dementia in AD and PD, the dose and side effects of L-dopa in PD; 3) to evaluate the usefulness of *CYP2D6* genotyping in predicting predispositions to PD and AD.

Material and methods: 53 patients with AD aged 58–84 (mean age 72.6) and 52 patients with PD with dementia aged 51–82 (mean age 70.4) were recruited. Each AD patient satisfied criteria for probable AD. Diagnostic and Statistical Manual of Mental Disorders 4th edition, Mini-Mental State Examination, Clinical Dementia Rating Scale and Global Deterioration Scale were used for dementia evaluation in PD patients. Clinical scales for PD evaluation were used. Methods of molecular biology were used for genetic studies.

Streszczenie

Wstęp i cel pracy: W etiopatogenezie sporadycznej choroby Alzheimera (ChA) i choroby Parkinsona (ChP) uwzględniana jest teoria dziedziczenia wieloczynnikowego, dlatego uważa się, że geny regulujące bioaktywację lub detoksyfikację egzogennych substancji mogą warunkować te schorzenia. Celem pracy było: 1) określenie genotypów cytochromu P450 2D6 (*CYP2D6*) u chorych z postacią sporadyczną ChA i ChP przebiegającą z otępieniem; 2) odpowiedź na pytanie, czy istnieje zależność pomiędzy genotypem *CYP2D6* a: wiekiem zachorowania oraz stopniem zaawansowania otępienia, natomiast w przypadku ChP dawką L-dopy i występowaniem powikłań leczenia, oraz 3) ocena przydatności genotypu *CYP2D6* w prognozowaniu zwiększonej predyspozycji do rozwoju ChA i ChP.

Materiał i metody: Przebadano 53 chorych na ChA w wieku 58–84 lata (średnia: 72,6 roku) i 52 pacjentów z ChP w wieku 51–82 lata (średnia: 70,4 roku). Wszyscy chorzy na ChA spełniali kryteria diagnostyczne prawdopodobnej ChA. W diagnostyce otępienia u chorych na ChP wykorzystano: DSM-IV, MMSE, Klinikzną Skalę Oceny Otępienia, Skalę Ogólnej Deterioracji. Stosowano kliniczne skale oceny ChP. Oznaczanie alleli *CYP2D6* przeprowadzono z wykorzystaniem metod zaproponowanych przez Smitha i wsp.

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Results: There were no differences in *CYP2D6* genotype and allele distribution in AD and PD patients. There was no relationship between *CYP2D6* alleles and the age of onset and advancement of dementia in AD and PD. No relationship between *CYP2D6* alleles and the dose and side effects of L-dopa in patients with sporadic PD with dementia was observed.

Conclusion: As there were no differences in *CYP2D6* polymorphism in AD and PD, *CYP2D6* does not seem to be a factor predisposing to these diseases.

Key words: *CYP2D6* gene polymorphism, Parkinson's disease, Alzheimer's disease, dementia.

Introduction

In recent years, there have been numerous reports indicating a genetic background of some diseases of the nervous system with still unexplained aetiology, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, multi-system atrophy, and dementia with Lewy bodies. It seems that the strong interest in those diseases results from the high and continuously increasing incidence and prevalence of AD and PD associated with a progressive process of elongation of population life span [1-12].

AD is a heterogeneous disease with regard to clinical, neuropathological, biochemical and molecular features. Two forms of the disease can be distinguished: the familial form, most frequently with early onset of symptoms, and the sporadic form, where the symptoms usually occur after the 65th year of life. Influence of hereditary factors is postulated both in the familial and sporadic form of AD. The sporadic form of AD constitutes 90% of all new cases of AD; therefore, detailed elucidation of its aetiology seems particularly important.

Genetic studies on AD with late onset conducted at the beginning of the nineteen nineties demonstrated its association with the *apolipoprotein E* (*ApoE*) gene located on chromosome 19q13.2 [13-16]. Three polymorphic forms of this gene, *E2*, *E3* and *E4*, were identified that are inherited co-dominantly and determine the occurrence of six genotypes: *E4/E4*, *E4/E3*, *E4/E2*, *E3/E3*, *E3/E2*, *E2/E2*. It was demonstrated that the main genetic risk factor increasing probability of AD occurrence is presence of the *E4* allele, whereas alleles *E2* and *E4* have a protective effect and markedly delay the onset of AD [15,16]. In 40% of cases of AD with late onset, no

Wyniki: Nie wykazano różnic w rozkładzie genotypów i alleli *CYP2D6*, zarówno u chorych na ChA, jak i na ChA w porównaniu z grupą kontrolną. Nie stwierdzono związku pomiędzy częstością występowania genotypów i alleli *CYP2D6* a wiekiem zachorowania i zaawansowaniem otępienia, natomiast u chorych z ChP z dawką L-dopy i występowaniem powikłań leczenia.

Wnioski: Polimorfizm genu *CYP2D6* nie jest czynnikiem ryzyka predysponującym do wystąpienia ani ChA, ani ChP przebiegającej z otępieniem.

Słowa kluczowe: polimorfizm genu *CYP2D6*, choroba Alzheimera, choroba Parkinsona, otępienie.

association between *ApoE* polymorphism and occurrence of the disease is observed [15]. This leads to a search for other genes potentially associated with AD. The group of candidate genes includes genes coding for metabolic activity of enzymes metabolising xenobiotics.

The enzymatic system of the microsomal hepatic fraction with its main component, cytochrome P450, is responsible for oxidation of multiple drugs and lipophilic, toxic compounds. The best known and clinically most significant isoenzyme among over 50 known isoenzymes of this cytochrome is *CYP2D6* (of the debrisoquine and spartenin type). Two phenotypically distinct groups were distinguished in the human population based on the capability to oxidise debrisoquine or spartenine to hydroxymetabolites: persons actively oxidating the mentioned compounds – extensive metabolisers (EM) – and persons oxidating poorly, to a minimum degree – poor metabolisers (PM) [17,18].

Apart from the wild type allele (WT), at least 8 alleles are currently known that determine the phenotype of slow oxidation [17-19]. Among PM in the Caucasian population, *CYP2D6*4* is the mutant allele with the highest frequency – 21%. In approximately 2% the *CYP2D6*3* allele is present, and in 4% *CYP2D6*5*. The remaining alleles are present in the Caucasian population relatively rarely, and have a higher frequency in the Asian population [18].

The association between increased incidence of AD and earlier manifestation of the disease in carriers of the *CYP2D6* allele determining the PM phenotype in homozygous persons is unclear [20-23].

In the development of sporadic form of PD, involvement of multiple polymorphic enzymes associated with detoxification of exogenous substances is postulated [1-4,6,8,11-13,24-29]. *CYP2D6* gene

polymorphism has been considered most important clinically. It is assumed that the PM genotype may be associated with the risk of occurrence and earlier manifestation of sporadic PD [6,7,29-35].

In recent years, the results of many clinical, pathological and epidemiological studies have been reported that suggest similar risk factors for PD and AD [36]. It is known that PD occurs mainly in elderly persons (mean age at disease onset is 58 years); however, dementia occurs concomitantly with PD significantly more frequently than expected based on these patients' age, while patients with AD often develop parkinsonian syndrome [15]. To pathologically establish definite diagnosis of PD, presence of Lewy bodies in the substantia nigra is required, and their presence in sites other than the substantia nigra is associated with dementia in PD [15]. Progress in immunohistochemical techniques has led to the finding that α -synuclein is the main fibrillary component of Lewy bodies both in PD and AD [15,37]. Apart from Lewy bodies, senile plaques and neurofibrillary tangles typical for AD are found in PD [36]. Some authors suggest that occurrence of cognitive dysfunction and dementia in PD patients is either a coexistence of diffuse Lewy body-type pathology or a coexistence of PD and AD [15]. In a search for a common pathogenetic link of sporadic PD and AD, the authors focused their attention on the significance of genetic variety in the catabolism of selected exogenous substances.

The aim of the study was: 1) to determine the genotype of the cytochrome P450 2D6 in patients with sporadic AD and sporadic PD with concomitant dementia, 2) to answer the question whether there is a relationship between the *CYP2D6* genotype and age at disease onset, severity of dementia, and – additionally in PD – levodopa dose and presence of complications of therapy, 3) to assess the prognostic value of the genotype *CYP2D6* in determining an increased predisposition for development of AD and PD.

Material and methods

Fifty-three patients with sporadic AD (19 males and 34 females), aged from 58 to 84 years (mean: 72.3 years), age at disease onset 57-80 years (69.2 years on average), and 52 of 184 patients with sporadic form of PD diagnosed according to the current criteria of the United Kingdom Parkinson's Disease Society Brain Bank [43], 26 males and 26 women, aged 51-82 years

(mean: 70.4 years), age at disease onset 42-78 years (mean: 61.5 years), were evaluated.

Diagnosis of PD was established based on the following information: history taken from the patient and his family, neurological and general medical examination, clinical observation, results of biochemistry and neuroimaging studies [computed tomography (CT), magnetic resonance imaging (MRI)]. Criteria described in the American Diagnostic and Statistic Manual of Mental Disorders, 4th edition (DSM-IV) served as a basis for diagnosis of dementia [5]. All patients fulfilled the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) [38]. Clinical Dementia Rating (CDR) scale and Global Deterioration Scale (GDS) were used to assess dementia severity [39]. Using the CDR scale, in 20 (37.7%) patients with AD, dementia was rated as mild, in 10 (18.9%) as moderate, and in 23 (43.4%) as severe. Using GDS, dementia was rated as moderate in 20 (37.7%) patients with AD, moderately severe in 8 (15.1%), severe in 6 (11.3%), and very severe in 19 (35.6%) patients. Exclusion criteria included: lack of consent to participate in the study, cerebral stroke, tumour, epilepsy, a history of head trauma, other concomitant disease potentially associated with dementia, chronic intake of drugs affecting cognitive processes, moderate to severe depressive episode (Beck Depression Inventory [9], Geriatric Depression Scale [41], and scores above 4 on the Hachinsky scale [42] were used to exclude patients with such a state).

All PD patients were treated with levodopa preparations at doses of 250-2000 mg/day, mean: 650.96 mg/day. Duration of levodopa treatment was 2-20 years (7.23 years on average). In each case, history was taken using a questionnaire designed in our department; neurological and general medical examination was performed. Biochemical and neuroimaging studies were performed in all patients (CT, MRI). To establish the diagnosis of dementia, four standardised criteria were used: DSM-IV, Mini Mental State Examination (MMSE) [44], CDR, and GDS. Mild dementia, according to the CDR scale, was diagnosed in 35 (67.3%) patients with PD, moderate in 11 (21.2%), and severe in 6 (11.5%) patients. Using GDS, moderate dementia was diagnosed in 35 (67.3%), moderately severe in 11 (21.2%), and severe dementia in 6 (11.5%) PD patients.

Patients who scored at least 1 on the CDR scale, at least 4 on GDS, had 23 or less points on MMSE, and who fulfilled both requirements of DSM-IV were enrolled in the study. Exclusion criteria were parallel to those used in the AD group; additionally, patients with dementia onset before or during the first two years of PD were excluded from the study. The following features were evaluated: disease severity and presence of therapy-related adverse events using the Unified Parkinson's Disease Rating Scale (UPDRS) [45], stage of the disease according to the Hoehn & Yahr scale [46], and activity of daily living using the Schwab & England scale [26].

Ninety healthy persons (43 males and 47 females), aged 65-86 years (mean age: 72.1 years), from the same population as the evaluated group, served as a control group. In all participants, history was taken and general medical and neurological examination and MMSE were performed, which allowed exclusion of persons with signs of central nervous system damage, including dementia (score below 24 in MMSE was the exclusion criterion).

Determination of the *CYP2D6* alleles – *CYP2D6*3*, *CYP2D6*4* and *CYP2D6*5* – was conducted according to the procedure proposed by Smith et al. [29]. Genomic DNA isolated from the peripheral blood was subjected to amplification using PCR with a pair of synthetic oligonucleotides, separately for the *CYP2D6*3* and *CYP2D6*4* mutations. The obtained product of amplification, after control assessment in 2% agarose gel, was subjected to digestion by restriction enzymes *BstNI* and *HpaII*. The *CYP2D6*3* mutation was evaluated using *HpaII* restrictase, which does not recognise the digestion locus in exon 5 in the normal genotype. The *CYP2D6*4* mutation was evaluated using *BstNI* restrictase, which recognises digestion locus in the wild allele. Separation of the obtained digestion products was conducted using electrophoresis in 8% polyacrylamide gel. The obtained bands corresponding to particular DNA fragments, following staining of the polyacrylamide gel with ethidine bromide, were analysed in UV light and recorded in graphical form.

To compare the variables among the groups, analysis of variance (ANOVA – for continuous variables/interval data) and χ^2 test (for categorical variables/nominal data) were used. Frequencies of the alleles were calculated based on the genotypes. Distribution of genotypes and frequency of *CYP2D6* alleles in the groups were compared using χ^2 test. Odds

ratio (OR) with 95% confidence interval (95% CI) was calculated by means of 2×2 contingency table or logistic regression. In the multivariable analysis, logistic regression and multiple models were used. For the estimation of factors of logistic regression equations, the quasi-Newton method was applied. Multiple regression analysis was conducted using the backward elimination procedure. The above-mentioned analyses were performed using the computer software Statistica 6.0 and Epi Info 6 (A Word Processing Database and Statistics Program for Public Health, ftp.cdc.gov), version 6.04.

Results

Among 53 patients with sporadic AD, EM homozygotes of the *CYP2D6*1* allele with *CYP2D6*1/CYP2D6*1* genotype constituted 67.92%, and heterozygotes with *CYP2D6*1/CYP2D6*4* genotype constituted 24.53%. Four (7.55%) persons were recessive homozygotes with genotypes *CYP2D6*3/CYP2D6*4* (1.89%) and *CYP2D6*4/CYP2D6*4* (5.66%). Results obtained in the AD group did not differ significantly from those of the control group (Table 1).

Frequency of *CYP2D6* gene alleles was compared between AD patients and the control group. Differences in allele frequency between the groups were not statistically significant (Table 2).

Among 52 patients with sporadic PD and concomitant dementia, dominant homozygotes of the allele *CYP2D6*1* – *CYP2D6*1/CYP2D6*1* constituted 84.62%, and heterozygotes with genotype *CYP2D6*1/CYP2D6*4* constituted 13.46%. One (1.92%) person was a recessive homozygote of the *CYP2D6*4* allele (Table 3).

Frequency of *CYP2D6* gene alleles was compared between PD patients and the control group. Differences in allele frequency between the groups were not statistically significant (Table 4).

Relationships between the *CYP2D6* alleles (*CYP2D6*1*, *CYP2D6*3*, *CYP2D6*4*) and the following variables were analysed: age at disease onset and dementia stage, and – in the case of PD patients – levodopa dose and presence of complications of anti-Parkinson treatment. No significant associations between the evaluated *CYP2D6* alleles and any of the analysed variables were found.

Table 1. Distribution of CYP2D6 genotypes in patients with Alzheimer's disease (AD) and controls

Genotypes		AD n (%)	Controls n (%)
Homozygote EM	CYP2D6*1/CYP2D6*1	36 (67.92)	62 (68.89)
Heterozygote IM	CYP2D6*1/CYP2D6*3	0	3 (3.33)
	CYP2D6*1/CYP2D6*4	13 (24.53)	23 (25.56)
Total		49 (92.45)	88 (97.78)
Homozygote PM	CYP2D6*3/CYP2D6*3	0	0
	CYP2D6*3/CYP2D6*4	1 (1.89)	1 (1.11)
	CYP2D6*4/CYP2D6*4	3 (5.66)	1 (1.11)
Total		4 (7.55)	2 (2.22)

$$\chi^2 = 2.49, p = NS$$

EM – extensive metabolisers, PM – poor metabolisers, IM – intermediary metabolisers

Table 2. Frequency of CYP2D6 alleles in patients with Alzheimer's disease (AD) and controls

Allele	AD n (%)	Controls n (%)	OR (95% CI)
CYP2D6*1	85 (80.19)	150 (83.34)	reference*
CYP2D6*3	1 (0.94)	4 (2.22)	0.44 (0.02 – 4.28)
CYP2D6*4	20 (18.87)	26 (14.44)	1.36 (0.68 – 2.7)
Total	106 (100.00)	180 (100.00)	

$$\chi^2 = 2.49, p = NS$$

EM – extensive metabolisers, PM – poor metabolisers, IM – intermediary metabolisers

Table 3. Distribution of CYP2D6 genotypes in patients with Parkinson's disease (PD) and controls

Genotypes		PD n (%)	Controls n (%)
Homozygote EM	CYP2D6*1/CYP2D6*1	44 (84.62)	62 (68.89)
Heterozygote IM	CYP2D6*1/CYP2D6*3	0	3 (3.33)
	CYP2D6*1/CYP2D6*4	7 (13.46)	23 (25.56)
Total		51 (98.08)	88 (97.78)
Homozygote PM	CYP2D6*3/CYP2D6*3	0	0
	CYP2D6*3/CYP2D6*4	0	1 (1.11)
	CYP2D6*4/CYP2D6*4	1 (1.92)	1 (1.11)
Total		1 (1.92)	2 (2.22)

$$\chi^2 = 4.48, p = NS$$

EM – extensive metabolisers, PM – poor metabolisers, IM – intermediary metabolisers

Table 4. Frequency of CYP2D6 alleles in patients with Parkinson's disease and controls

Allele	PD n (%)	Controls n (%)	OR (95% CI)
CYP2D6*1	95 (91.35)	150 (83.34)	reference*
CYP2D6*3	0	4 (2.22)	-
CYP2D6*4	9 (8.65)	26 (14.44)	0.55 (0.23-1.29)
Total	104 (100.00)	180 (100.00)	

$$\chi^2 = 4.60, p = NS$$

* with regard to wild allele

Discussion

Introduction of genetics and molecular biology into research of the nervous system, technical development that enabled identification of brain regions responsible for cognitive functions, tracking the pathways between particular parts of the brain, observation of neuronal activity, and assessment of receptors for various neurotransmitters have resulted in the fact that a search for the molecular basis of diseases constitutes the dominant tendency in medical research. However, despite numerous studies, pathomechanisms associated with PD and AD are not completely known. Currently, it is considered that sporadic AD and PD are diseases associated with multiple factors; genetic factors with superimposed effects of exogenous factors play an important role in the development of these diseases [8,26,47]. The theory of multifactorial aetiopathogenesis of sporadic AD and PD assumes that the disorders develop in a situation of exposure of a genetically susceptible person to harmful environmental factors. Therefore, genes regulating bioactivation or detoxification of exogenous substances are considered as potential factors augmenting susceptibility for these diseases. The finding of polymorphic DNA changes in patients with AD and PD that were more frequent than in the control group has led to considerations that they are indirectly or directly associated with the development of the diseases [1,6,20,21,25,28].

The system of monooxygenases with its principal component – cytochrome P450 – is the key system responsible for the process of oxygenation of multiple drugs and other xenobiotics. The isoenzyme *CYP2D6*, whose gene was localised to q13 on chromosome 22, is the best described isoenzyme so far and is clinically most important [18]. Studies on *CYP2D6* gene DNA polymorphism have gathered more attention than any other gene coding for a detoxification enzyme. It is hypothesised that it is the PM genotype that favours environmental toxin-induced damage to central nervous system cells by prolongation of the time of exposure to neurotoxins [8,26,47].

Association of increased incidence of AD and earlier development of the disease in PM-causing *CYP2D6* allele carriers has proven to be controversial [7,10,20,21,23,28].

Protective effects of the *CYP2D6*4* allele in AD was suggested in a report by Yamada et al. [22]. A study by Woo et al. [23] in a Korean population of AD patients ruled out the protective role of

*CYP2D6*4*. A study of five candidate genes conducted by Nicholl et al. [28] did not demonstrate significant differences in the number of PM in patients with AD as compared to the control group. Association of *CYP2D6* gene polymorphism with AD was also ruled out in studies by Murphy et al. [21], Benitez et al. [10] and Atkinson et al. [7]. Cervilla et al. [20] not only demonstrated a lack of differences in the prevalence of PM between AD and the control group but did not find any significant differences in age at disease onset or severity of dementia between PM and EM among AD patients either.

Similarly, like the majority of researchers, we did not find a relationship between *CYP2D6* gene polymorphism and sporadic AD in our population. We did not demonstrate differences in age at disease onset or dementia severity between PM and EM patients. It is therefore plausible that PM is not a risk factor for AD in the majority of Caucasians and – probably – in the majority of Asians.

In 1985, Barbeau and Roy [8] suggested that PM may have increased susceptibility to PD because of impaired detoxification. They based their theory on the fact that patients with PD significantly more frequently showed partial or complete impairment of debrisoquine hydroxylation than the control group. Two years later, the same research group confirmed the presence of the above trend and proved that PM are at risk of earlier development and more severe course of the disease [26]. Since then, numerous studies on association of the *CYP2D6* polymorphism with the risk of PD development in various populations have been conducted. Allelic variants of *CYP2D6* – *CYP2D6*3*, *CYP2D6*4* have inconsistently been linked by various authors to increased risk of PD [2,6,29,31,33] or increased risk of early onset PD [1] (Table 5), or such an association has been ruled out [2,3,12,24,30].

Reports published by Canadian [34], French [12], Swedish [47], Finnish [48] and Spanish [10] authors do not confirm such a correlation in their studied populations. It is, therefore, accepted that PM does not increase the risk of PD in the majority of the white population and probably in the majority of Asians. Our study confirmed this opinion: it did not show statistically significant differences in the distribution of genotypes and alleles of *CYP2D6* in patients with PD and concomitant dementia, as compared to our control group. In the available literature, we did not find studies on *CYP2D6* gene polymorphism in PD patients with coexisting dementia, with the exception of

Table 5. Relationship between the status of poor metabolisers (PM) and risk of Parkinson's disease (PD)

Author	Population	Analysis of CYP2D6	PD PM (%)	Controls PM (%)	OR (95% CI)
Armstrong et al., 1992	not described	AG*	3.77	2.77	1.38 (0.18-10.24)
Barbeau et al., 1985	French Canadians	APh**	10	7.5	1.36 (0.29-6.36)
Benitez et al., 1990	not described	APh	2.22	0.54	0.49 (0.13-1.80)
Chiba et al., 1993	Japanese	APh	0	2.38	0.15 (0.01-2.51)
Kallio et al., 1991	Finnish	APh	4.12	5.11	0.80 (0.25-2.57)
Smith et al., 1992	British	AG	11.79	5.0	2.99 (1.64-5.43)
Agundez et al., 1995	Spanish	AG	1.63	3.33	0.51 (0.11-2.28)
Gasser et al., 1996	Germans	AG	6.09	4.11	1.48 (0.40-5.44)
Lucotte et al., 1996	French	AG	10.64	2.13	4.09 (0.79-2.12)

*AG – analysis of genotype

**APh – analysis of phenotype

a report by Hubble et al. [50]. The study of Hubble et al. [50] demonstrated that the probability of development of PD with concomitant dementia increases to 83% in carriers of at least one *CYP2D6**4 allele, who had been exposed to pesticides. Perhaps, to confirm such relationship in our material, our sample size would need to be increased, which might have augmented the credibility of our results, although this credibility cannot be excluded, and the discrepancies may result from exposure of our population to other toxic factors. The association of the *CYP2D6* genotype with age at onset of PD has been evaluated by few authors in the available literature. Chiba et al. [51] and Benitez et al. [10] reported a statistically significant, although weak, association between age at disease onset and metabolism of debrisoquine and spartenine. According to Steiger et al. [35], Smith et al. [29], Armstrong et al. [6] and Cerville et al. [20], there is no association between oxidative capability and age at PD onset. Our analysis did not demonstrate any association between *CYP2D6* polymorphism and patients' age at onset of PD or AD. The results obtained by Chiba et al. may be related to different distribution of *CYP2D6* genotypes in the Asian population. We did not find any association between *CYP2D6* alleles and levodopa dose or presence of

complications of anti-Parkinson therapy. The results of our study unequivocally suggest that the assessed DNA changes in the *CYP2D6* gene are not a risk factor for AD or PD.

Conclusions

1. No differences in the distribution of *CYP2D6* genotypes and alleles were found among patients with sporadic AD and PD with concomitant dementia.
2. An association between the frequency of *CYP2D6* alleles and age at disease onset or dementia severity in patients with AD and PD was not confirmed; there was no association between *CYP2D6* alleles and levodopa dose or presence of complications of anti-Parkinson therapy.
3. Analysis of *CYP2D6* gene polymorphisms is not useful in prediction of an increased risk for AD or PD with concomitant dementia.

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