Genetic polymorphisms of CYP2D6 oxidation in patients with systemic sclerosis

Jadwiga Skrętkowicz, Malgorzata Baranska, Mariola Rychlik-Sych

Eur J Clin Pharmacol (2009) 65:971–976
DOI 10.1007/s00228-009-0662-3

PHARMACOGENETICS

Genetic polymorphisms of CYP2D6 oxidation in patients with systemic sclerosis

Jadwiga Skrętkowicz · Malgorzata Baranska · Mariola Rychlik-Sych

Received: 11 February 2009 / Accepted: 27 April 2009 / Published online: 15 May 2009

Abstract
Background Involvement of genetic and environmental factors in the pathogenesis of scleroderma has contributed to a number of studies whose aim is to elucidate the way in which xenobiotics exert effects on the occurrence of autoimmune processes resulting in development of systemic sclerosis (SSc).
Objective The study dealt with the evaluation of the genetically determined polymorphism of CYP2D6, one of the phase I drug metabolizing isoenzymes, in patients suffering from SSc. Usefulness of the *CYP2D6* genotype examination and prevalence of *CYP2D6* gene mutation in light of susceptibility to SSc development were assessed.
Methods Forty-three patients with SSc and 129 healthy volunteers were included in the study. Of the 43 patients with SSc, 17 fulfilled the criteria of diffuse SSc (dSSc) and 26 of limited SSc (lSSc). The determination of the *CYP2D6* oxidative polymorphism was performed with the PCR-RFLP method.
Results Relative risk of SSc development for particular genotype carriers expressed by the odds ratio (OR) was statistically significantly higher for subjects with *CYP2D6*1/CYP2D6*4* (OR=4.8; $P<0.001$). A statistically significant correlation between the *CYP2D6*4* allele prevalence and the risk for developing SSc was found (OR=2.6; $P=0.0002$).
Conclusion Higher prevalence of the *CYP2D6*4* mutated alleles in patients with SSc and the obtained OR values suggest that this mutation has the effect of increasing SSc morbidity rate.

J. Skrętkowicz (✉) · M. Baranska · M. Rychlik-Sych
Department of Pharmacogenetics, Medical University of Łódź,
Muszyńskiego 1,
90-151 Lodz, Poland
e-mail: jskretkowicz@pharm.am.lodz.pl

Keywords Genetic polymorphism · Oxidation · *CYP2D6* · Systemic sclerosis (SSc)

Introduction

In recent years, numerous studies concerning the association of drug-metabolizing enzyme polymorphism with autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), dermatitis herpetiformis (DH), and mixed connective tissue diseases (MCTD) have been carried out [1–9].

The current knowledge on the pathomechanism of autoimmune diseases indicates that many etiological factors may have a genetic background [10–16].

In the course of systemic sclerosis, several factors suggest the involvement of a genetic component: a relationship between the disease's prevalence and the gender; familial case reports; frequent coexistence of autoimmune diseases or immune phenomena in the families of patients suffering from SSc; higher prevalence of the disease in some ethnic groups; as well as the results of investigations on the system of antigen tissue compatibility; association with polymorphism of genes encoding extracellular matrix components, signaling molecules, and cytokines; studies concerning chromosomal fragility phenomenon; and genetically conditioned animal models of this disease [17–19]. Recently, studies on the association between the prevalence of SSc and the polymorphism of numerous genes have been conducted. In patients from Japan and the Choctaw Indian tribe, single nucleotide polymorphisms (SNP) within the FBN-1 gene were more frequently observed than in controls; however, Wipff et al. did not find similar changes in French and Italian populations [20, 21]. A higher density of CD19 in B

lymphocytes (approximately 20%) was reported in patients with SSc, as compared to a general population, whereas a single nucleotide mutation, G499T, in the CD19 receptor was found to indicate a high risk for developing SSc in a Japanese population [22, 23]. Moreover, the polymorphism of genes encoding angiotensin-converting enzyme (ACE) and mutations within the genes encoding receptors for IL—1B, IL—2, and IL—10 were investigated in SSc patients [24–26].

Environmental factors have been known to play a crucial role in scleroderma, therefore numerous studies are being performed whose aim is to elucidate the effect of xenobiotics on the occurrence of autoimmune processes leading to SSc development. Many xenobiotics may induce alterations in the chromosomal structure, e.g., drugs, pesticides, fungicides, or substances causing environmental pollution [27]. The studies on etiopathogenesis of autoimmune diseases focus on the impact the genetically conditioned impairment of xenobiotic metabolism may exert. Many enzymes of cytochrome P450, including CYP2D6, play an instrumental role in the oxidation of multiple drugs and in the activation and deactivation of environmental xenobiotics. The knowledge of oxidation polymorphism in the course of SSc may be helpful in choosing more efficient and safer therapy, particularly in the case of a disease involving various organs and treated with drugs belonging to diverse therapeutic groups. The aim of the present work was to assess the genetically determined *CYP2D6* polymorphism, one of the izoenzymes of phase I drug metabolism in patients suffering from systemic sclerosis. The usefulness of *CYP2D6* genotype study and the prevalence of *CYP2D6* gene mutation were determined to evaluate susceptibility to SSc development.

Materials and methods

The study was carried out in 43 patients with SSc diagnosed according to the criteria of the American College of Rheumatology. The group of patients with SSc consisted of 34 women and 9 men (age range 17–76 years, mean 54± 12.94). In 17 patients, diffuse SSc (dSSc) was diagnosed, and 26 patients fulfilled the criteria for limited SSc (lSSc). The patients were treated at the Department of Dermatology and Venereology, Medical University of Lodz. The control group consisted of 129 healthy volunteers (80 women, 49 men) aged 18–73 years (mean age 41.3±15.41). The local Ethics Committee for Scientific Research approved the study, and informed consent was obtained from all patients.

The identification of the *CYP2D6* gene alleles (*CYP2D6*1*, *CYP2D6*3*, *CYP2D6*4*) was performed according to the procedure described by Smith et al. [28].

The application of the PCR-RFLP method allowed two phenotypically distinct oxidation groups of subjects to be isolated: poor metabolizers (PM), which were homozygotes possessing two mutated alleles: *CYP2D6*3* and *CYP2D6*4*; and extensive metabolizers (EM), which were heterozygotes possessing one wild-type allele (*CYP2D6*1*) and one mutated allele (*CYP2D6*3, CYP2D6*4*) or homozygotes possessing two wild alleles (*CYP2D6*1)* in their loci.

The frequency distribution of *CYP2D6* genotypes in SSc patients was compared with healthy subjects and analyzed statistically using the χ^2 test alone and with the Yates modification for small groups. The odds ratio (OR) with 95% confidence interval (95% CI) was calculated using the computer program Statistica 6.0.

Results

The frequency distributions of oxidation genotypes determining poor and extensive metabolizers in patients suffering from systemic sclerosis and in the control group were similar: 11.6 and 9.3%, 88.4 and 90.7%, respectively. There were no statistically significant differences in the prevalence of *CYP2D6* genotypes determining poor and extensive oxidation between the two groups (P=0.8827) (Table 1). In separating the SSc patients into the two subsets, we did not find any association with oxidation genotype in patients from the dSSc and lSSc groups (P=0.6417; P=0.3524) (Table 1).

The *CYP2D6*1/CYP2D6*4* genotype was most frequently found in the group of patients with SSc (67.4%),

Table 1 Distribution of genotypes determining poor and extensive oxidation in patients with systemic sclerosis (SSc), diffuse systemic sclerosis (dSSc), limited systemic sclerosis (lSSc), and in controls

Oxidative genotype	Control group (n=129)	SSc (n=43)			lSSc (n=26)			dSSc (n=17)		
	n (%)	n (%)	χ^2	P	n (%)	χ^2	P	n (%)	χ^2	P
Poor	12 (9.3)	5 (11.6)	0.20	0.8827	4 (15.4)	0.86	0.3524	1 (5.9)	0.22	0.6417
Extensive	117 (90.7)	38 (88.4)			22 (84.6)			16 (94.1)		

P Statistical significance of the difference (statistically significant differences $P<0.05$), χ^2 test comparing two groups

while the *CYP2D6*1/CYP2D6*1* genotype predominated in the control group (57.4%). Among SSc patients, the dominating homozygotes (*CYP2D6*1/CYP2D6*1*) accounted for 16.3%; in the control group, these homozygotes accounted for 57.4%. The differences were statistically significant ($P<0.001$). Heterozygotes with one mutated and one wild-type allele constituted a considerably higher percentage (72.1%) in the SSc patients than in the controls (33.3%); these differences were statistically significant ($P<0.001$). The percentage of mutated homozygotes was slightly higher in the SSc patients (11.6%) as compared to the controls (9.3%), however, the difference was statistically insignificant ($P=0.8827$). The relative risk for SSc development expressed by the odds ratio (OR) was 4.8-fold higher for subjects with the *CYP2D6*1/CYP2D6*4* genotype ($P<0.001$) (Table 2). The relative risk for developing lSSc and dSSc in particular genotype carriers, expressed as the odds ratio (OR), was statistically significantly higher for subjects with the *CYP2D6*1/CYP2D6*4* genotype (OR=3.7, $P=0.0023$; OR=7.5, $P=0.0002$) (Table 2).

Among 86 alleles studied in patients with SSc, the mutated alleles accounted for 47.7%, and the wild one accounted for 52.3%. Among 258 alleles in the control group, the mutated alleles, *CYP2D6*, accounted for 26%, and the wild ones accounted for 74%. A statistically significant correlation was found between the prevalence of the *CYP2D6*4* allele and the risk for developing SSc (OR=2.6; $P=0.0002$) and also between the prevalence of the *CYP2D6*4* allele and the risk for developing lSSc (OR=2.7; $P=0.0015$) and dSSc (OR=2.4; $P=0.0147$) (Table 3).

Table 2 Frequency distribution of *CYP2D6* alleles in the group of patients with systemic sclerosis (SSc), diffuse systemic sclerosis (dSSc), limited systemic sclerosis (lSSc), and in the controls

CYP2D6 groups	Control group ($n=129$)	SSc ($n=43$)			lSSc ($n=26$)			dSSc ($n=17$)		
	n (%)	*n* (%)	OR (95% CI)	χ^2 (*P*)	*n* (%)	OR (95% CI)	χ^2 (*P*)	*n* (%)	OR (95% CI)	χ^2 (*P*)
Extensive oxidation genotype: homozygotes *CYP2D6*1/CYP2D6*1*	74 (57.4)	7 (16.3)	0.14 (0.06–0.33)	21.85 (<0.001)	4 (15.4)	0.14 (0.05–0.37)	15.21 (<0.0001)	3 (17.6)	0.16 (0.05–0.51)	9.51 (<0.002)
Extensive oxidation genotype: heterozygotes *CYP2D6*1/CYP2D6*3*	4 (3.1)	2 (4.7)	1.5 (0.27–8.54)	0.23 (0.035)	2 (7.7)	2.6 (0.48–14.13)	1.23 (0.2682)	0	–	–
*CYP2D6*1/CYP2D6*4*	39 (30.2)	29 (67.4)	4.8 (2.35-9.72)	18.68 (<0.001)	16 (61.5)	3.7 (1.59-8.58)	9.26 (<0.0023)	13 (76.5)	7.5 (2.61-21.55)	14.0 (0.0002)
Poor oxidation genotypes *CYP2D6*3/CYP2D6*4*	0	0	–	–	0	–	–	0	–	–
*CYP2D6*4/CYP2D6*4*	12 (9.3)	5 (11.6)	1.3 (0.43–3.82)	0.20 (0.8827)	4 (15.4)	1.8 (0.53–5.95)	0.86 (0.3524)	1 (5.9)	0.6 (0.08–4.83)	0.22 (0.6417)

P Statistical significance of the difference (statistically significant differences $P<0.05$), χ^2 test comparing two groups, *C.I.* confidence interval, *OR* odds ratio

Discussion

The human organism is constantly exposed to harmful exogenous factors (xenobiotics), including drugs and carcinogenic compounds that can induce development of a large number of diseases. The processes of biotransformation in the organisms are multidirectional and xenobiotics can be transformed into active or inactive metabolites through oxidative routes. They can be changed into harmful compounds with a potentially pathogenic action. The enzymatic system of the liver microsomal fraction with cytochrome P450 as its fundamental element is responsible for xenobiotic oxidation. Cytochrome P450 enzymes show genetic polymorphism, which contributes to considerable interindividual differences in drug responses. Studies of the oxidative genotype or phenotype have been performed in order to identify the oxidative polymorphism.

Differences among individuals in drug response due to mutations within the *CYP2D6* gene involved in the xenobiotic metabolism, including a number of drugs with a wide therapeutic use, were discovered as early as the

Table 3 Frequency distribution of particular alleles in the group of patients with systemic sclerosis (SSc), diffuse systemic sclerosis (dSSc), limited systemic sclerosis (lSSc), and in the controls

Allele	Control group (n=129)	SSc (n=43)			lSSc (n=26)			dSSc (n=17)		
	n (%)	n (%)	OR (95% CI)	χ^2 (P)	n (%)	OR (95% CI)	χ^2 (P)	n (%)	OR (95% CI)	χ^2 (P)
*CYP2D6*1*	191 (74)	45 (52.3)	0.38 (0.23–0.63)	12.8 (0.0002)	26 (50.0)	0.35 (0.19–0.64)	11.90 (0.0006)	19 (55.9)	0.45 (0.22–0.91)	4.90 (0.0269)
*CYP2D6*3*	4 (1.6)	2 (2.3)	1.5 (0.28–8.19)	0.23 (0.6344)	2 (3.8)	2.5 (0.48–13.46)	1.20 (0.2730)	0	–	–
*CYP2D6*4*	63 (24.4)	39 (45.4)	2.6 (1.55-4.24)	13.55 (0.0002)	24 (46.2)	2.7 (1.45–4.84)	10.13 (0.0015)	15 (44.1)	2.4 (1.19–5.01)	5.95 (0.0147)

P Statistical significance of the difference (statistically significant differences $P<0.05$), χ^2 test comparing two groups, *C.I.* confidence interval, *OR* odds ratio

1970s. Genetically determined oxidative polymorphism can affect not only drug efficacy but can also be a factor predisposing to disease development [29–36].

There are few reports in the available literature that concern the role of oxidative polymorphism in autoimmune diseases, however no studies have dealt with the *CYP2D6* genotype in the course of systemic sclerosis.

First investigations on the association between the oxidative genotype and autoimmune diseases were conducted in the 1990s. Studies have demonstrated that oxidative polymorphism is not associated with the risk factor for systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) development [1, 2, 8].

In our own studies on the *CYP2D6* genotype in SSc, we observed a similar percentage of individuals who were characterized by poor metabolism among SSc patients in comparison with healthy controls. No statistically significant differences in the prevalence of *CYP2D6* genotypes for poor and extensive oxidation were found between the groups studied (P=0.8827). The relative risk for developing SSc in particular genotype carriers, expressed as the odds ratio (OR), was statistically significantly higher for subjects with the *CYP2D6*1/CYP2D6*4* genotype (OR=4.8; $P<0.001$). A relative risk for developing SSc was 2.6-fold higher in *CYP2D6*4* allele carriers and was statistically significant (P=0.0002).

A higher prevalence of mutated *CYP2D6*4* alleles in patients with SSc suggests the effect of mutation on an increased frequency of two forms of SSc—limited SSc (lSSc) and diffuse SSc (dSSc).

The effect of *CYP2D6* gene mutation on the risk of disease development has awakened a lot of interest in researchers. The polymorphism of this gene may be associated with the subjects' predisposition to neurological diseases [29, 36]. The studies carried out by Butler et al. demonstrate a higher risk for development of colorectal cancer (OR=3.34) in women possessing the *CYP2D6*1* allele in their genotype, which determines extensive oxidation [35].

There are reports in the literature presenting the influence of the polymorphism of other cytochrome P450 enzymes on the risk of SSc development. Povey et al. revealed that the *CYP2E1*3* allele of cytochrome P450, one of the phase I izoenzymes, was more frequently found in patients with systemic sclerosis who had been exposed to organic solvent (trichloroethylene, trichloroethane) activity as compared to healthy subjects. Such a correlation was not observed in the group of patients with an idiopathic form of SSc [37]. In other investigations also concerning the phase I xenobiotic metabolism, a reduced ability of dapsone and S-mephenitoin hydroxylation was reported in SSc patients, whereas there was no difference in the activity of debrizochin hydroxylase between this group and

controls. May et al. evaluated that the relative risk of SSc development was 10-fold higher (P=0.008) in patients with poor metabolism of mephenitoin and dapsone. This complex metabolic impairment may contribute to SSc development, or, on the other hand, the pathological process could be solely responsible for inhibition of selected enzymes metabolizing xenobiotics in some groups of patients [1]. Investigating the distribution of *CYP1A1* polymorphisms, von Schmiedeberg et al. did not observe significant differences among SSc patients in comparison to a healthy population [2].

Genetic factors play a significant role in the etiopathogenesis of systemic sclerosis. Knowledge of the genetically conditioned differences in oxidation processes as well as determination of the prevalence of the main mutations in the cytochrome P450 izoenzyme *CYP2D6* gene seems to be of vital clinical importance.

Acknowledgements This work was supported by grant No. 502-18-665 and No. 503-8011-1 from the Medical University of Lodz, Poland.

References

1. Sabbagh N, Marez D, Queyrel V, Lo Guidice J-M, Spire C, Vanhille P, Jorgensen C, Hachulla E, Broly F (1998) Genetic analysis of cytochrome P450 CYP2D6 polymorphism in patients with systemic lupus erythematosus. Pharmacogenetics 8(3):191–194
2. Kortunay S, Bozkurt A, Bathum L, Basci NE, Calgüneri M, Brøsen K, Kayaalp SO (1999) CYP2D6 polymorphism in systemic lupus erythematosus patients. Eur J Clin Pharmacol 55 (1):21–25
3. Zschieschang P, Hiepe F, Gromnica-Ihle E, Roots I, Cascorbi I (2002) Lack of association between arylamine N-acetyltransferase 2 (NAT2) and systemic lupus erythematosus. Pharmacogenetics 12(7):559–63
4. Skrętkowicz K, Skrętkowicz J, Gawrońska-Szklarz B, Górnik W, Rychlik-Sych M, Sysa-Jędrzejowska A (2005) Lack of association between arylamine N-acetyltransferase 2 (NAT2) polymorphism and systemic sclerosis. Eur J Clin Pharmacol 60(11):773–778
5. Soejima M, Sugiura T, Kawaguchi Y, Kawamoto M, Katsumata Y, Takagi K, Nakajima A, Mitamura T, Mimori A, Hara M, Kamatani N (2007) Association of the diplotype configuration at the N-acetylotransferase 2 gene with adverse events with cotrimoxazole in Japanese patients with systemic lupus erythematosus. Arthritis Res Ther 9(2):R23
6. Rychlik-Sych M, Skrętkowicz J, Gawrońska-szklarz B, Górnik W, Sysa-Jędrzejowska A, Skrętkowicz-Szarmach K (2006) Acetylation genotype and phenotype in patients with systemic lapus erythematosus. Pharmacol Rep 58(1):22–29
7. Pawlik A, Ostanek L, Brzosko I, Dąbrowska-Zamojcin E, Gawrońska-Szklarz B (2004) The influence of N-acetyltransferase 2 polymorhism on rheumatoid arthritis activity. Clin Exp Rheumatol 22(1):99–102
8. Beyeler C, Daly AK, Armstrong M, Astbury C, Bird HA, Idle JR (1994) Phenotype/genotype relationships for the cytochrome P450 enzyme CYP2D6 in rheumatoid arthritis: influence of drug therapy and disease activity. J Rheumatol 21(6):1034–39
9. Rychlik-Sych M, Skrętkowicz-Szarmach K, Gawrońska-Szklarz B, Górnik W, Skrętkowicz J (2006) Polimorfizm NAT2 w wybranych chorobach o podłożu autoimmunologicznym. Prob Ter Monit 17 (4):239–244
10. May DG, Black CM, Olsen NJ, Csuka ME, Tanner SB, Bellino L, Porter JA, Wilkinson GR, Branch RA (1990) Scleroderma is associated with differences in individual routes of drug metabolism, a study with dapsone, debrisoquine, and mephenytoin. Clin Pharmacol Ther 48(3):286–95
11. von Schmiedeberg S, Fritsche E, Ronnau AC, Specker C, Golka K, Richter-Hintz D, Schuppe HC, Lehmann P, Ruzicka T, Esser C, Abel J, Gleichmann E (1999) Polymorphisms of the xenobiotic-metabolizing enzymes CYP1A1 and NAT-2 in systemic sclerosis and lupus erythematosus. Adv Exp Med Biol 455:147–152
12. Tan FK, Arnett FC (2000) Genetic factors in the etiology of systemic sclerosis and Raynaud phenomenon. Curr Opin Rheumatol 12:511–19
13. Stephens CO, Briggs DC, Whyte J, Artlett CM, Scherbakov AB, Olsen N, Gusseeva NG, McHugh NJ, Maddison PJ, Welsh KI (1994) Familial scleroderma - evidence for environmental versus genetic trigger. Br J Rheumatol 33(12):1131–35
14. Skrętkowicz J, Skrętkowicz-Szarmach K (2006) Uwarunkowania genetyczne w patogenezie twardziny układowej. Pol Merk Lek XX(115):117–120
15. Johnson RW, Tew MB, Arnett FC (2002) The genetics of systemic sclerosis. Curr Rheumatol Rep 4(2):99–107
16. Skrętkowicz J, Skrętkowicz-Szarmach K, Rychlik-Sych M (2004) Genetyczne uwarunkowania w patogenezie tocznia rumieniowatego układowego. Reumatologia 42(4):567–572
17. Englert H, Small-McMahon J, Chambers P, O'Connor H, Davis K, Manolios N, White R, Dracos G, Brooks P (1999) Familiar risk estimation on systemic sclerosis. Aust NZ J Med 29(1):36–41
18. Arnett FC, Cho M, Chatterjee S, Aquilar MB, Reveille JD, Mayes MD (2001) Familial occurrence frequencies and relative risk for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis Rheum 44(6):1359–62
19. De Keyser F, Peene I, Joos R, Naeyaert JM, Messiaen L, Veys EM (2000) Occurrence of scleroderma in monozygotic twins. J Rheumatol 27(9):2267–69
20. Tan FK, Wang N, Kuwana M, Chakraborty R, Bona CA, Milewicz DH, Arnett FC (2001) Association of fibrillin 1 single nucleotide polymorphism haplotypes with systemie sclerosis in Choctaw and Japanese populations. Arthritis Rheum 44(4):893–901
21. Wipff J, Giraud M, Sibilia J, Mouthon L, Meyer O, Tiev K, Airo P, Caramaschi P, Guiducci S, Garchon HJ, Matucci-Cerinic M, Kahan A, Avouac J, Boileau C, Allanore Y (2008) Polymorphic markers of the fibrillin-1 gene and systemic sclerosis in European Caucasian patients. J Rheumatol 35(4):643–49
22. Sato S, Hasegawa M, Fujimoto M, Tedder TF, Takehara K (2000) Quantitative genetic variation in CD19 expression correlates with autoimmunity. J Immunol 165(11):6635–6639
23. Tsuchiya N, Kuroki K, Fujimoto M, Murakami Y, Tedder TF, Tokunada K, Takehara K, Sato S (2004) Association of a functional CD19 polymorphism with susceptibility to systemie sclerosis. Arthritis Rheum 50(12):4002–7
24. Bartoli F, Angotti C, Fatini C, Conforti ML, Guiducci S, Blagojevic J, Melchiorre D, Fiori G, Generini S, Damjanov N, Rednic S, Pignone A, Castellani S, Abbate R, Matucci Cerinic M (2007) Angiotensin-converting enzyme I/D polymorphism and macrovascular disease in systemic sclerosis. Rheumatology 46 (5):772–75
25. Mattuzzi S, Barbi S, Carletto A, Ravagnani V, Moore PS, Bambara LM, Scarpa A (2007) Association of polymorphism in

the IL1B and IL2 genes with susceptibility and severity of systemic sclerosis. J Rheumatol 34(5):903–5
26. Beretta L, Cappiello F, Barili M, Scorza R (2007) Proximal interleukin-10 gene polymorphism in Italian patients with systemic sclerosis. Tissue Antigens 69(4):305–12
27. Arlett CM, Black CM, Briggs DC, Stevens CO, Welsh KI (1996) Telomere reduction in scleroderma patients, a possible cause of chromosomal instability. Br J Rheumatol 35(8):732–37
28. Smith CA, Gough AC, Leigh PN, Summers BA, Harding AE, Maraganore DM, Sturman SG, Schapira AH, Williams AC (1992) Debrisoquine hydroxylase gene polymorphism and suscebility to Parkinsons disease. Lancet 339(8806):1375–1377 6
29. Gołąb-Janowska M, Honczarenko K, Gawrońska-Szklarz B, Potemkowski A (2007) *CYP2D6* gene polymorphism as a probable risk factor for Alzheimer's disease and Parkinson's disease with dementia. Neurol Neurochir Pol 41(2):113–121
30. Ledesma MC, Aqundez JAG (2005) Identification of subtypes of CYP2D gene rearrangements among carriers of CYP2D6 gene deletion and duplication. Clin Chem 51(6):939–943
31. Sobti RC, Onsory K, Al-Badran AI, Kaur P, Watanabe M, Krishan A, Mohan H (2006) CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population. DNA and Cell Biology 25(5):287–294
32. Sobti RC, Al-Badran AI, Sharma S, Sharma SK, Krishan A, Mohad H (2005) Genetic polymorphisms of *CYP2D6*, *GSTM1*, and *GSTT1* genes and bladder cancer risk in North India. Cancer Genet Cytogenet 156(1):68–73
33. Perera FP, Deliang T, Brandt-Rauf P, Santella RM, Mooney VA, Tu Y-H, Bendkowska I, Bell DA (2006) Lack of associations among cancer and albumin adducts, ras p21 oncoprotein levels, and CYP1A1, CYP2D6, NAT1, and NAT2 in nested case-control study of lung cancer within the Physicians' Health Study. Cancer Epidemiol Biomarkers Prev 15:1417–1419
34. Lapiński L, Agundez JAG, Wiela-Hojeńska A, Ganczarski G, Orzechowska-Józwenko K, Wołowiec D, Głowacka K, Kuliczkowski K (2007) CYP2D6 gene amplification and the risk of acute myeloblastic leukemia. Pharmacol Rep 59 (1):167–172
35. Butler WJ, Ryan P, Roberts-Thomson IC (2001) Metabolic genotypes and risk for colorectal cancer. J Gastroenterol Hepatol 16(6):631–635
36. Woo S, Kim JW, Seo HG, Park CH, Han SH, Kim SH, Kim KW, Jhoo JH, Woo JI (2001) CYP2D6*4 polymorphism is not associated with Parkinson's disease and has no protective role against Alzheimer's disease in the Korean population. Psych Clin Neurosci 55(4):373–377
37. Povey A, Guppy MJ, Wood M, Knight C, Black CM, Silman AJ (2001) Cytochrome P2 polymorphism and susceptibility to scleroderma following exposure to organic solvents. Arthritis Rheum 44(3):662–65