Original paper

# Genetic polymorphisms of CYP2D6 oxidation in patients with autoimmune bullous diseases

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## Abstract

**Introduction:** Bullous skin diseases, which include, among others pemphigoid, pemphigus, and dermatitis herpetiformis are classified as severe autoimmune dermatoses. It has been shown that a pattern of xenobiotic metabolism may play a role in the pathogenesis of autoimmune diseases.

**Aim:** To estimate whether the *CYP2D6* genotype may be considered a predisposing factor in autoimmune bullous diseases induction.

**Material and methods:** The study included 72 patients with autoimmune bullous diseases: 37 with pemphigoid, 21 with pemphigus, and 14 with dermatitis herpetiformis (DH). The *CYP2D6* genotypes were analyzed by the polymerase chain reaction fragment length polymorphism (PCR-RFLP) method.

**Results:** Relative risk of DH development for particular genotype carriers expressed by odds ratio (OR) was statistically significantly higher for subjects with *CYP2D6*1/CYP2D6*4* (OR = 4.2; $p$ = 0.0104) and 2-fold higher for subjects with CYP2D6*4 (OR = 2.3; $p$ = 0.0351).

**Conclusions:** The results of the present study show that the CYP2D6 oxidation polymorphism cannot be considered a risk factor for development of pemphigoid and pemphigus, however it might have an impact on dermatitis herpetiformis.

**Key words:** genetic polymorphism, CYP2D6, pemphigoid, pemphigus, dermatitis herpetiformis.

## Introduction

Bullous skin diseases, including pemphigoid, pemphigus, and dermatitis herpetiformis are considered severe autoimmune dermatoses. These diseases are characterized by bullae and bullous eruptions on the skin and within the mucosa. Depending on the site of bulla formation in the epidermis, bullous diseases are divided into intraepidermal (acantholytic), which comprise all types of pemphigus, and subepidermal ones including pemphigoid and dermatitis herpetiformis [1–3].

Pemphigoid (bullous pemphigoid – BP) is the most frequently occurring entity among bullous diseases. It develops mainly in the elderly people, and the relative risk of its prevalence at the age of 90 years is nearly 300-fold higher than at the age of 60 [4].

Genetic involvement in pemphigoid has not been clarified so far. The association with HLA DR4, DR5, and DQw3 antigens implies a role of genetic factors in etiopathogenesis of this disease. Pemphigoid may be also induced by orally administered drugs, e.g. furosemide or novoscabin applied topically to the skin [1, 5].

Pemphigus occurs in two basic forms: pemphigus vulgaris (PV) and pemphigus foliaceus (PF), which differ in the clinical picture and depth of acantholysis formation (damage to the connections between keratinocytes). Pemphigus belongs to genetically conditioned diseases with a dominating way of inheritance. There are some reports on familial prevalence of this disease and the relationship with HLA DR*4, DRw6, and DQw8. Cases of pemphigus concomitant with other autoimmune diseases, e.g. rheumatoid arthritis, sys-

temic lupus erythematosus, or pemphigoid, have been observed [6–9]. Moreover, effects of environmental factors on pemphigus development have been also considered. In some cases, drugs (penicillin, captopril, butapirazol), sunlight, skin burns, viral (Herpetoviridae family) infections and some foods, e.g. garlic, leek, onion (containing a thiol group responsible for induction of chemical acantholysis) may become disease-provoking factors [1, 9].

Dermatitis herpetiformis (DH) is a chronic bullous disease. Due to concomitance with intestinal hypersensitivity, Duhring's disease is classified as cutano-intestinal syndrome. It most often afflicts young white men and children. Familial predisposition to DH has been emphasized; siblings more often suffer from this disease than parents and children. In DH pathogenesis, the relationship with HLAB8, DR3, DQw2, and DR2 is frequently mentioned [1, 10–12].

Bullous skin diseases develop as a result of disorders of the tolerance to self-antigens. Acantholytic bullous dermatoses are characterized by the presence of antibodies directed against desmosomal structures (bridges connecting keratinocytes) and surface antigens of keratinocytes, whereas subepidermal bullous dermatoses induce antigens against semidesmosomal/hemidesmosomal structures and the basement membrane [2].

The pathomechanism of developing cutaneous lesions in the course of bullous skin diseases has not been completely known so far. Similar to other autoimmune diseases, the role of genetic and environmental factors has been emphasized in etiopathogenesis of bullous diseases. The genetic factor involvement has been implied by their higher prevalence among patients' relatives, the relationships with HLA alleles, tissue compatibility antigens and polymorphism of numerous genes coding complement constituents, some receptors and cytokines.

Due to the significant role that environmental factors play in the pathogenesis of autoimmune diseases, various studies have been carried out to explain the way in which xenobiotics may affect the occurrence of autoimmune processes leading to the development of these diseases. Many xenobiotics such as drugs, pesticides, fungicides or substances that cause environmental pollution may induce changes in the chromosomes structure, leading to genetic mutations [13–15]. Xenobiotics involved in initiation of pathological processes of autoimmune diseases, similarly to all xenobiotics, undergo metabolic processes in the human body.

Among numerous enzymes involved in xenobiotic metabolism, the enzymatic system of hepatic microsomal fraction, the so-called monooxygenase system (multifunctional monooxygenase, mixed function oxygenase – MFO), whose main component is cytochrome P-450 enzymes, is responsible for oxidation processes belonging to phase I metabolism. Currently, the role of cytochrome P-450 and its isoenzymes have been considered significant both in regulating drug metabolism and determining other functions of the organism, such as inducing the immunological response or the processes, which are responsible for activation of toxic substances.

Cytochrome P-450 enzymes demonstrate the genetic polymorphism caused by the presence of mutation in the gene responsible for synthesis of a particular enzymatic protein. The mutation occurrence leads to individual variability of isoenzyme metabolic activity manifesting through a lack, reduction, or increased activity of the enzyme.

CYP2D6, called debrisoquine hydroxylase, is one of the best-known significant clinical cytochrome P-450 isoenzymes manifesting genetic variability. The gene responsible for the expression of CYP2D6 enzyme is located on chromosome 22q13.1 [16, 17]. Approximately 100 *CYP2D6* alleles have been identified, among which over 20 significantly change metabolism of drugs that are substrates of this enzyme [18, 19]. Depending on the metabolic rate, a human population has been divided into: extensive metabolizers (EM), ultrarapid metabolizers (UM), intermediate metabolizers (IM), and poor metabolizers (PM). Poor metabolizers genotype corresponds to a homozygous genotype of two recessive genes responsible for impaired metabolism, while extensive metabolizers of xenobiotics may be homozygotes carrying two genes conditioning fast oxidation phenotype or heterozygotes possessing one gene responsible for slow, and another one for fast oxidation. Ultrarapid metabolizers additionally have a greater number of active genes at the same locus [16, 19].

The studies assessing susceptibility to develop diseases in extensive metabolizers indicated a higher prevalence of pulmonary and genitourinary neoplasms as well as acute myeloblastic leukemia in these subjects. While among poor metabolizers, an increase in the prevalence of Parkinson's disease and epilepsy was observed; however, the results of different groups of researchers are not coherent [20–25]. Literature reports on the relationship between CYP2D6 fast oxidation and the prevalence of various diseases, mostly neoplastic and neurological, have encouraged researchers to look for such relations also in dermatological diseases.

Recently, an interest in the role of polymorphism of enzymes metabolizing xenobiotics in systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), regarded as autoimmune diseases, has risen [26–36]. However, reports on the polymorphism of enzymes metabolizing xenobiotics in bullous skin diseases are scarce and mostly concern the genetic polymorphism of thiopurine methyltransferase (TPMT) and N-acetyltransferase 2 (NAT2) involved in the metabolism of drugs administered in the treatment of these diseases [37–41].

An attempt was made in the present study to assess genetically determined polymorphism of CYP2D6, which is one of the isoenzymes mediating phase I drug metabolism in patients suffering from skin bullous diseases. Moreover, the usefulness of CYP2D6 genotype investigation and the prevalence of CYP2D6 gene mutation were determined to evaluate susceptibility to bullous disease development,

including pemphigoid, pemphigus, and dermatitis herpetiformis.

## Material and methods

The study comprised 72 patients with skin bullous diseases: 37 with pemphigoid, 21 with pemphigus, and 14 with dermatitis herpetiformis. There were 40 women and 32 men aged 19–92 years (mean age 60.6 ±21.36 years). All patients were treated at the Department of Dermatology and Venereology at the Medical University of Lodz.

Pemphigoid was diagnosed based on the clinical picture, and histological and immunological findings. The patients were at an active stage of the disease, 30 out of 37 patients were presented with skin blisters, vesicles and itching papules, whereas others had only small vesicles and urticarial papules. In all the patients, the direct immunofluorescence test revealed IgG/C3 linear deposits along BMZ. In the salt split test, deposits were observed in the epidermal part of the blister. Using the indirect immunofluorescence test, circulating IgG antibodies were found in 33/37 patients. Whereas the ELISA test showed the anti-Nc16 autoantibodies (MBL, Nagoya, Japan) present in serum of 35 out of 37 patients. Typical histological features of BP including neutrophilic infiltrates, eosinophils, lymphocytes and in 35 cases – subepidermal blisters supported the clinical diagnosis.

Pemphigus was diagnosed based on the clinical picture, and histological and immunological findings. The patients were at an active stage of the disease, 18 out of 21 patients were presented with skin blisters, vesicles and erythema, whereas others had only small vesicles and erosions. In all the patients, the direct immunofluorescence test revealed IgG/C3 deposits form a network-like pattern. Using the indirect immunofluorescence test, circulating pemphigus antibodies were found in 19/21 patients.

The study included untreated patients with DH in an active stage of the disease. Ten out of 14 patients had skin lesions characterized by vesicles and itching papules, the others had erythematous papules. In all cases histological pictures showed perivascular neutrophilic infiltrates, the presence of Pierrard's abscesses, and in all patients small subepidermal blisters. In 10/14 samples, large unilocular blisters displaying multiple neutrophilic papillary microabscesses were found. Direct immunofluorescence tests revealed the presence of granular deposits of IgA in skin papillae and indirect immunofluorescence tests were positive for IgAEmA (Oesophagus monkey IgAEmA, Medizinische Labordiagnostica) in all the patients (titer 1 : 10 − 1 : 320, median 1 : 40). Anti-tissue transglutaminase antibodies measured using an immunoassay (Celikey, Pharmacia & Upjohn) were present in 6/14 cases (median 4.3 IU/ml, range: 0.0–156.3 IU/ml). Diagnosis of DH was established based on clinical presentation and results of histological and immunological examinations.

The control group included 129 healthy volunteers, 80 women and 49 men aged between 18 and 73 years (mean age 41.3 ±15.41). The study was approved by the University Bioethics Committee for Research on Human Subjects.

Identification of the *CYP2D6* gene alleles (*CYP2D6*1, CYP2D6*3, CYP2D6*4*) was performed by using the PCR-RFLP method according to the procedure described by Smith *et al.* [42]. Genomic DNA isolated from peripheral blood leukocytes according to Gustincich *et al.* [43] was amplified using the PCR method with a pair of synthetic oligonucleotides, separately for *CYP2D6*3* and *CYP2D6*4* mutations. To detect the presence or absence of mutations at position A1934T (*CYP2D6*4* mutation) and deletions at position A2637 (*CYP2D6*3* mutation), the obtained product of PCR amplification was subjected to digestion by restrictive enzymes BstN1 (New England BioLabs, USA) (*CYP2D6*4* mutation) and Hpa II (Invitrogen USA) (*CYP2D6*3* mutation). The separation of digestion products was carried out in 8% polyacrylamide gel. The received stripes reflecting particular DNA fragments were visualized in UV light after ethidium bromide staining.

### Statistical analysis

Statistical analysis was performed by using the $\chi^2$ test. A relative risk of disease development was determined by calculating odds ratio (OR) with the appropriate confidence level and the use of Statistica 9.1 software.

### Results

The study results indicated that the frequency distribution of extensive and poor metabolizers in the group of

**Table 1.** Frequency distribution of poor and extensive metabolizers in patients with pemphigoid (BP), pemphigus and dermatitis herpetiformis (DH) and in the controls

| Oxidation genotype | Control group (N = 129) n (%) | Bullous diseases (N = 72) | | | BP (N = 37) | | | Pemphigus (N = 21) | | | DH (N = 14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n (%) | $\chi^2$ | p | n (%) | $\chi^2$ | p | n (%) | $\chi^2$ | p | n (%) | $\chi^2$ | p |
| Poor | 12 (9.3) | 6 (8.3) | 0.05 | 0.8176 | 4 (10.8) | 0.0017 | 0.9666 | 0 | 1.05 | 0.3061 | 2 (14.3) | 0.02 | 0.9025 |
| Extensive | 117 (90.7) | 66 (91.7) | | | 33 (89.2) | | | 21 (100) | | | 12 (85.7) | | |

*p – significantly lower (p < 0.05), $\chi^2$ – test comparing two groups*

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**Table 2.** Frequency distribution of particular CYP2D6 genotypes in patients with pemphigoid (BP), pemphigus and dermatitis herpetiformis (DH) and in the controls

| CYP2D6 | Control group (N = 129) n (%) | Bullous diseases (N = 72) | | | BP (N = 37) | | | Pemphigus (N = 21) | | | DH (N = 14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) |
| Extensive oxidation genotype: homozygotes CYP2D6*1/CYP2D6*1 | 74 (57.4) | 40 (55.6) | 0.93 (0.56–1.55) | 0.06 (0.8040) | 23 (62.2) | 1.2 (0.57–2.53) | 0.27 (0.6017) | 14 (66.7) | 1.5 (0.57–4.01) | 0.64 (0.4221) | 3 (21.4) | 0.2 (0.53–0.76) | 5.20 (0.0226) |
| Extensive oxidation genotype: heterozygotes | | | | | | | | | | | | | |
| CYP2D6*1/ CYP2D6*3 | 4 (3.1) | 0 | – | 0.97 (0.3258) | 0 | – | 0.23 (0.6339) | 0 | – | 0.01 (0.9302) | 0 | – | 0.03 (0.8533) |
| CYP2D6*1/ CYP2D6*4 | 39 (30.2) | 26 (36.1) | 1.3 (0.71–2.39) | 0.73 (0.3930) | 10 (27.1) | 0.86 (0.38–1.95) | 0.14 (0.7063) | 7 (33.3) | 1.15 (0.43–3.06) | 0.08 (0.7751) | 9 (64.3) | 4.2 (1.32–13.46) | 6.57 (0.0104) |
| Poor oxidation genotype: | | | | | | | | | | | | | |
| CYP2D6*3/ CYP2D6*3 | 0 | 1 (1.4) | – | 0.09 (0.7669) | 1 (2.7) | – | 0.45 (0.5042) | 0 | – | – | 0 | – | – |
| CYP2D6*3/ CYP2D6*4 | 0 | 2 (2.8) | – | 1.35 (0.2455) | 1 (2.7) | – | 0.45 (0.5042) | 0 | – | – | 1 (7.14) | – | 1.84 (0.1745) |
| CYP2D6*4/ CYP2D6*4 | 12 (9.3) | 3 (4.1) | 0.42 (1.16–1.52) | 1.10 (0.2944) | 2 (5.4) | 0.56 (0.19–2.64) | 0.17 (0.6771) | 0 | – | 1.05 (0.3061) | 1 (7.14) | – | 0.05 (0.8240) |

p – significantly lower (p < 0.05), $\chi^2$ – test comparing two groups, CI – 95% confidence interval, OR – odds ratio

**Table 3.** Frequency distribution of particular CYP2D6 alleles in patients with pemphigoid (BP), pemphigus and dermatitis herpetiformis (DH) and in the controls

| Alleles | Control group (N = 129) n (%) | Bullous diseases (N = 72) | | | BP (N = 37) | | | Pemphigus (N = 21) | | | DH (N = 14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) | n (%) | OR (95% CI) | $\chi^2$ (p) |
| CYP2D6*1 | 191 (74) | 106 (73.6) | 0.98 (0.61–1.57) | 0.01 (0.9268) | 56 (75.7) | 1.1 (0.6–1.86) | 0.08 (0.7751) | 35 (83.3) | 1.8 (0.76–4.26) | 1.68 (0.1947) | 15 (53.6) | 0.4 (0.18–0.89) | 5.25 (0.0220) |
| CYP2D6*3 | 4 (1.6) | 4 (2.8) | 1.8 (0.44–7.39) | 0.22 (0.6366) | 3 (4.0) | 2.6 (0.57–12.06) | 0.74 (0.3884) | – | – | 0.01 (0.9306) | 1 (3.6) | 2.3 (0.25–21.33) | 0.0002 (0.9873) |
| CYP2D6*4 | 63 (24.4) | 34 (23.6) | 0.96 (0.6–1.54) | 0.03 (0.8560) | 15 (20.3) | 0.79 (0.42–1.48) | 0.55 (0.4581) | 7 (16.7) | 0.6 (0.25–1.42) | 1.21 (0.2707) | 12 (42.8) | 2.3 (1.03–5.1) | 4.44 (0.0351) |

p – significantly lower (p < 0.05), $\chi^2$ – test comparing two groups, CI – 95% confidence interval, OR – odds ratio

patients suffering from bullous skin diseases including pemphigoid, pemphigus, and dermatitis herpetiformis was similar to the control group (Table 1).

Table 2 shows the results of examination of *CYP2D6* genotype in patients with bullous skin diseases. The *CYP2D6*1/CYP2D6*1* genotype was most frequently found among the patients with bullous diseases including pemphigoid and pemphigus as well as in the control group (55.6%, 62.2%, 66.7%, and 57.4%, respectively). However, in the group of patients with dermatitis herpetiformis, the percentage of the dominating homozygotes was lower (21.4%) than in the control group (57.4%). The differences were statistically significant ($p$ = 0.0226). The patients with dermatitis herpetiformis most frequently had the *CYP2D6*1/CYP2D6*4* genotype (64.3%), whereas in the control group its prevalence was 30.2%; the differences being statistically significant ($p$ = 0.0104). The relative risk of developing dermatitis herpetiformis expressed by the odds ratio was over 4 times higher for subjects with the *CYP2D6*1/CYP2D6*4* genotype (OR = 4.2; $p$ = 0.0104).

Based on the results of genotyping, the frequency distribution of particular alleles of the *CYP2D6* gene was assessed in the group of patients with bullous skin diseases including pemphigoid, pemphigus, and dermatitis herpetiformis, as well as in the controls (Table 3). In all groups of patients as well as in the control group, the wild-type *CYP2D6*1* allele was most common (73.6%, 75.7%, 83.3%, 53.6%, 74.0%, respectively). The variant wild-type *CYP2D6** allele occurred more rarely only in the patients with dermatitis herpetiformis (53.6%) as compared to the controls (74.0%); the differences were statistically significant $p$ = 0.0220). Whereas, the mutated *CYP2D6*4* allele was significantly more often present among the patients with dermatitis herpetiformis than in the control group (42.8%, 24.4%, respectively, $p$ = 0.0351). The relative risk of developing dermatitis herpetiformis expressed by the odds ratio was 2-fold higher in subjects in whom the presence of the *CYP2D6*4* allele (OR = 2.3; $p$ = 0.0351) was identified.

The relative risk of developing bullous skin diseases, including pemphigoid, pemphigus, and dermatitis herpetiformis, expressed by the OR was found to be higher for carriers of the mutated *CYP2D6*3* allele (1.8, 2.6, and 2.3, respectively). The risk, however, appeared to be statistically insignificant ($p$ = 0.6366, $p$ = 0.3884, $p$ = 0.9873).

## Discussion

In the process of drug biotransformation, a significant role has been attributed to cytochrome P-450 enzymes (CYP). The CYP enzymes show genetic polymorphism that leads to structural changes in coded proteins and modification of their activity. Differences in metabolic processes induced as a result of the presence of mutated alleles explain individual variability of responses to the same drug. They may also contribute to mutagenic and carcinogenic alterations in DNA and activation of toxic substances, thus initiating various pathogenic processes in the human organism.

Etiopathogenesis of numerous skin diseases has not been elucidated to date. The contemporary knowledge related to this subject reveals the presence of numerous factors affecting their development and suggests the role of genetic and environmental factors. Nowadays more attention has been drawn to the involvement of cytochrome P-450 and its isoenzymes in the course of dermatological diseases.

The studies on CYP2D6 polymorphism carried out among patients suffering from atopic diseases and psoriasis suggest an increase in the prevalence of the diseases in extensive metabolizers.

Recently, the CYP2D6 oxidation polymorphism has been observed to have an impact on the prevalence of atopic diseases, particularly bronchial asthma and allergic rhinitis. Nearly a 3-fold higher relative risk of development (OR = 2.81) of these diseases was reported in EM subjects and almost 2-fold higher relative risk (OR = 1.85) of the extensive *CYP2D6* genotype [44].

In the investigations carried out among patients suffering from psoriasis a more frequent prevalence of the disease has been stated in extensive metabolizers. The relative risk of psoriasis development was higher (OR = 1.22) in EM subjects as compared to subjects with intermediate and poor *CYP2D6* genotype [45].

In recent years, the interest of researchers has been drawn to the role of oxidation polymorphism in autoimmune diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) [31–36]. Since both systemic as well as environmental factors have been shown to be involved in pathogenesis of these diseases, it is likely that polymorphisms of xenobiotic metabolizing enzymes including the polymorphism of CYP2D6 isoenzyme are associated with the immune system dysfunction that contributes to the development of autoimmune diseases.

The first reports on the relationship between the *CYP2D6* genotype oxidation and autoimmune diseases were published in the 1990s.

The studies carried out among the patients with SLE demonstrated that the prevalence of *CYP2D6*4* allele was considerably higher in comparison to the control group (28.3% and 18.6%, respectively). However, the difference was not statistically significant. The *CYP2D6*4* allele was observed to occur more often in SLE patients in whom renal or hematological lesions had been observed [35].

Polymorphism of CYP2D6 in SLE patients was also the subject of the study by Kortunay *et al.* The authors did not indicate any differences in the prevalence of particular genotypes in the group of SLE patients and in controls [36].

Similarly, Skrętkowicz *et al.* revealed that CYP2D6 polymorphism was not a risk factor for developing SLE. A slightly higher percentage of PM individuals (13.3%) among SLE patients was observed as compared to healthy people (9.3%); however, the differences were statistical-

ly insignificant. Moreover, no statistically significant differences in *CYP2D6* genotypes determining slow and fast oxidation in both groups studied were found [31]. Although the results of these studies show that the CYP2D6 oxidation polymorphism is not a risk factor for SLE development, the determination of the *CYP2D6* genotype is of great clinical importance. Systemic lupus erythematosus is a multi-organ disease and there is often a need for administering drugs belonging to different therapeutic groups, including those that metabolize with the involvement of CYP2D6. The results of therapy with drugs undergoing oxidation are less satisfactory in extensive metabolizers as compared to poor metabolizers. High activity of CYP2D6 enzyme does not allow to reach therapeutic concentration of the drug, while low CYP2D6 enzyme activity and the associated slow metabolism increase the risk of adverse actions after administering a standard dose. Thus, the study of oxidation polymorphism may contribute to efficient and safe therapy.

There are scarce reports in the available literature presenting the influence of the polymorphism of cytochrome P-450 enzymes on the risk of SSc, which is characterized by a chronic autoimmune inflammatory process.

The study performed in the group of patients with SSc showed a statistically significant correlation between the prevalence of particular *CYP2D6* genotypes and the risk of SSc. The relative risk of SSc development expressed by the odds ratio was over 5-fold higher for carriers of the *CYP2D6*1/CYP2D6*4* genotype (OR = 4.8, $p < 0.001$) determining the extensive metabolism and 3-fold higher for carriers of the mutated *CYP2D6*4* allele (OR = 2.6; $p = 0.0002$) [32]. The results of the research suggest that the CYP2D6 oxidation polymorphism can be considered a risk factor for SSc development.

In our own studies concerning the effect of polymorphism in gene coding CYP2D6 enzyme on the prevalence of bullous skin diseases including pemphigoid, pemphigus, and dermatitis herpetiformis (DH), statistically significant correlations between the prevalence of the *CYP2D6* genotype and the risk of DH development were observed. The relative risk of DH expressed by the OR was significantly higher for carriers of the *CYP2D6*1/CYP2D6*4* genotype (OR = 4.23, $p = 0.0104$). Moreover, a higher prevalence of the *CYP2D6*4* allele was found in patients with DH as compared to the controls. The estimated relative risk of DH development expressed by the OR was 2-fold higher in *CYP2D6*4* allele carriers (OR = 2.3); this risk was statistically significant ($p = 0.0351$).

The results of the present study show that the *CYP2D6* oxidation polymorphism cannot be considered a risk factor for development of pemphigoid and pemphigus, however it might have an impact on dermatitis herpetiformis. The research on the CYP2D6 oxidation polymorphism should be continued because there are no reports in the available literature presenting the effect of this polymorphism on the development of bullous skin diseases.

Numerous researchers have emphasized the role of polymorphism of xenobiotic metabolizing enzymes including the CYP2D6 oxidation polymorphism as a risk factor for various diseases. The interest has been more often drawn to autoimmune diseases due to their complex and not entirely elucidated etiology. The studies concerning polymorphism of xenobiotic metabolizing enzymes in the course of bullous skin diseases may contribute to greater efficacy and safety in pharmacotherapy and determine susceptibility to develop these diseases.

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