

PTPN22 Polymorphism Presumably Plays a Role in the Genetic Background of Chronic Spontaneous Autoreactive Urticaria

Z. Brzoza^a W. Grzeszczak^b B. Rogala^a W. Trautsolt^b D. Moczulski^c

^aChair and Clinical Department of Internal Diseases, Allergology and Clinical Immunology, and ^bChair and Clinical Department of Internal Diseases, Diabetology and Nephrology, Medical University of Silesia, Katowice, and ^cChair and Clinical Department of Internal Diseases and Nephrodiabetology, Medical University of Łódź, Łódź, Poland

Key Words

Chronic urticaria · Polymorphism · PTPN22

Abstract

Background: The association of chronic urticaria (CU) with autoimmune disorders is relatively well proved. Protein tyrosine phosphatase-22 (PTPN22) is considered to be one of the strongest genetic factors for human autoimmunity. We decided to evaluate whether additional, non 1858C>T, PTPN22 variants are independent contributors to the risk of CU occurrence in the Polish population. **Methods:** A total of 91 CU patients with a positive result of autologous serum skin test and 100 healthy volunteers were enrolled in the study. The Urticaria Activity Score was used in disease intensity assessment. In all subjects rs3811021, rs1310182 and rs2488457 polymorphisms were genotyped. **Results:** We found a higher prevalence of –1123 C allele among CU patients. No differences in the allele and genotype distribution were found in the other analyzed polymorphisms. Haplotype construction of the three SNPs revealed statistically significant CU association of rs2488457C, rs1310182T and rs3811021T. **Conclusions:** Contrary to previous findings, the contribution of PTPN22 to disease susceptibility is suggested. We can speculate that CU is a genetically complex disease and that its occurrence needs multiple genetic and environmental risk factors.

Copyright © 2012 S. Karger AG, Basel

Introduction

Chronic urticaria (CU) is a debilitating skin disorder with a profound impact on quality of life [1]. In some conditions it can be even life-threatening in the form of upper airway angioedema. The pathogenesis of CU is not well understood. Its pathophysiology includes immune and inflammatory components as well as hormonal abnormalities [2–4]. Besides, there is a concept of its autoimmune origin. About 35–50% of CU patients suffer from autoimmune urticaria. Autoimmune origin of urticaria is connected with IgG anti-IgE antibodies or antibodies directed against the high-affinity IgE receptor (FcεR1) [5]. Autologous serum skin test (ASST) is positive in 50–60% of active CU patients. The negative result of this test is a valuable marker of the absence of circulating functional autoantibodies [6].

A strong association was proved between autoimmune CU and major histocompatibility complex class allele [7]. In the O'Donnel et al. study [7] HLA II allele frequencies combination in CU patients with positive ASST and positive histamine release from basophils was correlated with DRBI*04 and totally different from allele frequencies in the group of patients with negative ASST. Such a relationship suggests the role of a genetic component in the pathogenesis of some types of urticaria. Moreover, in such a way autoimmune urticaria seems to be associated

Table 1. Previously suggested disease associations of analyzed PTPN22 polymorphisms

SNP	Disease [reference]
rs3789604	RA [28]
rs1310182	RA [28]
rs2488457	T1D, RA [30, 31, 43]

with HLA alleles related to other autoimmune diseases. The coexistence of CU with thyroid autoimmunity is relatively well proved [8–14]. Asero et al. [15] reported an association of urticaria with Raynaud's phenomenon and anticentromere antibodies. Besides, there were some suggestions concerning a possible link between the presence of the rheumatoid factor and urticaria [16]. Anti-endothelial cell antibodies were also suspected in the pathogenesis of urticaria. Those antibodies were also found in lupus erythematosus and urticarial vasculitis [17].

Susceptibility to autoimmune disorders seems to be predominantly associated with genetic, epigenetic and environmental factors. Their genetic basis is gradually being uncovered [18]. Protein tyrosine phosphatase-22 (PTPN22), located at 1p13.3–p13.1, is considered to be the strongest genetic factor for human autoimmunity besides major histocompatibility complex [19]. PTPN22 encodes Lyp, hematopoietic phosphatase negatively regulating TCR signaling by dephosphorylating the activating tyrosine of the Src family kinase Lck [20, 21]. Polymorphism in the PTPN22 (1858C>T) was proved to be associated with some autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis (RA) and type 1 diabetes (T1D) risk occurrence [22–24]. Additionally, it was shown to be related to Graves disease and Hashimoto thyroiditis [25, 26].

In our previous study we proved no dependency on CU and PTPN22 1858C>T polymorphism [27]. As there are suggestions questioning whether the 1858C>T exonic SNP represents the only autoimmunity-predisposing SNP within the PTPN22 gene (particularly in the context of ethnic restrictions), Carlton et al. [28] reported evidence for additional SNPs, namely rs3811021 (3' untranslated region), rs3789604 and rs1310182 (intron 16) associated with autoimmunity independently of the 1858C>T.

Another possibly 'independent' PTPN22 SNP is promoter polymorphism rs2488457 (–1123G>C) located in the promoter region [29]. In previous studies rs2488457 was associated with acute-onset T1D [30]. Additionally, it was proved to be involved in the pathogenesis of RA in the Chinese population [31] (table 1).

Since several forms of autoimmunity have been associated with CU, we decided to evaluate whether additional, non 1858C>T, PTPN22 variants are independent contributors to the risk of CU occurrence in the Polish population. The project was approved by the Ethical Committee of the Medical University of Silesia.

Subjects and Methods

Study Sample Characteristics

A total of 91 unrelated CU patients (64 females and 27 males, mean age 38.1 years, range 21–58 years) with a positive result of ASST were enrolled in the study. The diagnosis of spontaneous type of urticaria without known eliciting factors and coexisting sensitizations was established on precise medical history, physical examination and skin tests. Mean disease duration was 26.9 ± 5.78 months. As a control 100 unrelated healthy volunteers (68 females and 32 males, mean age 46.1 years, range 19–59 years) were studied.

In disease intensity analysis we used the Urticaria Activity Score (UAS), a tool based on the assessment of wheals and pruritus in CU, and according to the current guidelines recommended in clinical practice, trials and therapy effectiveness analyses [32, 33]. According to the indications suggesting documentation of a patient self-perception score for several days, we performed a one-week assessment yielding a total score of 0–42 (UAS7). Additionally, in all CU patients disease onset age was analyzed.

Genomic DNA Isolation and PTPN22 Genotyping

EDTA blood samples were obtained from all examined subjects. Genomic DNA was extracted from peripheral blood leukocytes using the MasterPure™ DNA Purification Kit (Epicentre Technologies, Madison, Wisc., USA), according to the manufacturer's instructions. We analyzed rs3811021, rs1310182 and rs2488457 polymorphisms. Genotyping was performed by allelic discrimination with Custom TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, Calif., USA) using 7300 real-time PCR System (Applied Biosystems).

Statistical Analysis

The χ^2 test was used for analysis of the statistical significance of the differences in allele and genotype frequencies between patients and controls. The Kruskal-Wallis test was applied for UAS7 and disease onset age comparisons among different genotype distribution subgroups. Statistical analyses were performed using Statistica 8.0 PL (StatSoft Inc., Tulsa, Okla., USA). The frequency of haplotypes was estimated using the package 'BayHap' of the software R version 2.11.1 (The R Foundation for Statistical Computing). The linkage disequilibrium between analyzed polymorphisms was calculated using the package 'genetics'.

Results

Hardy-Weinberg equilibrium analysis discovered no deviation either in the CU or in the control group. The genotype and allele frequencies for the analyzed poly-

Table 2. PTPN22 genotype and allele distribution in CU patients and healthy controls

SNP	Group	Genotype distribution, total number (%)			Allele, total number (%)		OR (95% CI)	p
rs2488457	CU	CC	CG	GG	C	G	1.59 (0.83–2.97) p' = 0.049	0.155
	controls	8 (9)	34 (37)	49 (54)	50 (27)	132 (73)		
		2 (2)	33 (33)	65 (65)	37 (18)	163 (82)		
rs1310182	CU	CC	CT	TT	C	T	1.33 (0.67–2.64) p' = 0.208	0.474
	controls	23 (25)	46 (51)	22 (24)	92 (51)	90 (49)		
		31 (31)	53 (53)	16 (16)	115 (57)	85 (43)		
rs3811021	CU	CC	CT	TT	C	T	1.27 (0.68–2.38) p' = 0.611	0.508
	controls	4 (4)	29 (32)	58 (64)	37 (20)	145 (80)		
		4 (4)	38 (38)	58 (58)	46 (23)	154 (77)		

OR = Odds ratio; CI = confidence interval; p = statistical significance (p' = allele frequency statistical significance). The OR was calculated for patients homozygous or heterozygous carrying risk allele vs. homozygous.

Table 3. PTPN22 haplotype distribution in CU patients and healthy controls

Haplo- types ^a	Control group ^b , frequency (95% CI)	CU ^c , frequency (95% CI)	p
GTT	1.5% (0.3–3.5%)	1.8% (0.5–4.1%)	ns
CCC	0.3% (0–0.8%)	0% (0–0.1%)	ns
GCT	56.9% (50.4–63.1%)	50.1% (43.4–57.1%)	ns
CTC	0.4% (0–1.7%)	0% (0%)	ns
GTC	22.6% (16.4–28.0%)	20.3% (14.8–26.4%)	ns
CCT	0.3% (0–1.2%)	0% (0%)	ns
GCT	0.1% (0–0.9%)	0% (0%)	ns
CTT	17.9% (13.1–22.7%)	27.8% (21.0–34.3%)	0.027

^a rs2488457, rs1310182, rs3811021. ^b 200 haplotypes. ^c 182 haplotypes.

CI = Confidence interval; p = statistical significance; ns = statistically nonsignificant.

Table 4. UAS one-week assessment (UAS7) (points) and disease onset age (years) in CU patients with rs2488457 different genotypes

	Genotype distribution			p
	CC	CG	GG	
UAS7	22.3 ± 7.11	20.2 ± 7.92	19.4 ± 8.03	ns
Disease onset age	38.5 ± 8.12	33.9 ± 5.83	35.2 ± 6.75	ns

Data are presented as mean ± standard deviation. p = Statistical significance; ns = statistically nonsignificant.

morphisms are presented in table 2. We found a statistically significantly higher prevalence of –1123 C allele among CU patients when compared to controls. The prevalence of C allele was 1.35-fold higher in the patient group. The frequency of the risk homozygous CC genotype was 9% in CU and 2% in the control group, with borderline statistical significance. No statistically significant differences in the allele and genotype distribution between CU patients and controls were found in the other analyzed polymorphisms. The analyzed rs2488457, rs1310182 and rs3811021 polymorphisms were in almost complete linkage disequilibrium (D' = 0.99). Haplotype construction of the three SNPs revealed eight haplotypes, of which rs2488457C, rs1310182T and rs3811021T showed statistically significant CU association (table 3).

No dependency between PTPN22 genotypes and the severity of urticaria or disease onset age was observed. We assumed it after the analysis of these parameters in patients with different genotype distributions (tables 4–6).

Discussion

In CU 35–50% of cases are of autoimmune origin. In this group we find patients with the most severe manifestations as this form is more resistant to therapy and presents a more aggressive course. The ASST is used in autoreactivity assessment. Autoreactivity detection in CU is described as itchy weal and flare in response to autolo-

Table 5. UAS one-week assessment (UAS7) (points) and disease onset age (years) in CU patients with rs1310182 different genotypes

	Genotype distribution			p
	CC	CT	TT	
UAS7	20.1 ± 6.61	21.9 ± 8.22	19.9 ± 6.97	ns
Disease onset age	32.9 ± 7.76	36.7 ± 6.72	38.0 ± 9.32	ns

Data are presented as mean ± standard deviation. p = Statistical significance; ns = statistically nonsignificant.

gous serum injection resulting from the presence of different serum histamine-releasing factors. To diagnose autoimmune urticaria, functional autoantibodies must be confirmed by in vitro laboratory histamine release tests [6, 33].

There are some immunological links between autoimmune urticaria and autoimmune disorders. Immuno-reactive non-histamine-releasing anti-FcεRIα autoantibodies were found in patients with RA, systemic lupus erythematosus, systemic sclerosis and dermatomyositis [34, 35]. In RA patients anti-IgE autoantibodies were found [34, 35]. Moreover, IgE in immune complexes was assumed to sensitize RA synovial mast cells [36].

As the occurrence of CU is frequently associated with autoimmune thyroid diseases and genetic susceptibility to autoimmune thyroid diseases is well proved, we speculated on a genetic background of CU [37–40]. PTPN22 was proved to be associated with a susceptibility to Graves disease and Hashimoto thyroiditis. On the other hand, no association was found in a study analyzing the dependency between PTPN22 and allergic asthma [41]. PTPN22 1858C>T is considered to be a significant marker for autoimmunity. The genetic data combined with biochemical evidence that this SNP affects PTPN22 function indicates that this phosphatase is a key regulator of autoimmunity. Although 1858C>T represents the main autoimmunity-related variant in the PTPN22 locus [23], the effect of this polymorphisms is limited to some diseases and populations. In some diseases 1858C>T only accounts for a small part of the linkage signal seen at chromosome 1p [22, 29]. Additionally, PTPN22 gene polymorphism shows ethnic differences [42].

Constantly, we further analyzed three other PTPN22 polymorphisms. As PTPN22 is generally connected with autoantibody production, we selected ASST-positive pa-

Table 6. UAS one-week assessment (UAS7) (points) and disease onset age (years) in CU patients with rs3811021 different genotypes

	Genotype distribution			p
	CC	CT	TT	
UAS7	19.2 ± 7.31	22.3 ± 5.99	20.4 ± 7.93	ns
Disease onset age	37.9 ± 6.93	33.4 ± 8.14	36.3 ± 7.53	ns

Data are presented as mean ± standard deviation. p = Statistical significance; ns = statistically nonsignificant.

tients because of the role of ASST as a marker of circulating functional autoantibodies [6]. We expected to find associations between CU and these polymorphisms as autoreactive urticaria is connected with the production of autoantibodies. In the present study we found a dependency between rs2488457 polymorphism and susceptibility to CU. We are the first to suggest and prove an association of rs2488457 polymorphism with CU susceptibility. Previously, this SNP was supposed to be related to autoimmunity, i.e. Kawasaki et al. [30] reported an association of rs2488457 polymorphism with acute-onset T1D. The results from the Onengut-Gumuscu et al. study [43] were similar. Moreover, this polymorphism was suspected to be related to RA. On the other hand, rs2488457 was not proved to be involved in T1D and juvenile idiopathic arthritis in the Czech population and in T1D in the Azeri population [44].

Although Carlton et al. [28] proved an association of rs1310182 and rs3811021 variants with autoimmunity-related diseases, no evidence of association with CU in the Polish population was found in our study. On the other hand, CTT haplotype combination of 2488457, 1310182 and 3811021 polymorphisms was proved to result in urticaria. This phenomenon is interesting as allele T of rs1310182 and allele C of rs3811021 were previously found to be associated with RA [28].

In our study the polymorphism different from 1858C>T PTPN22 was proved to be implicated in the susceptibility to CU with positive ASST in the Polish population. Contrary to our previous findings the contribution of PTPN22 to disease susceptibility has been suggested [27]. Similarly to the study on 1858C>T, in other PTPN22 variants we did not observe any influence of analyzed genotypes on disease intensity as well as disease onset age [27].

Keeping in mind similarities between autoreactive and autoimmune urticaria, in the light of our results we can suppose a similar genetic profile in both subtypes of CU, though this hypothesis needs further exploration. We can speculate that CU is a genetically complex disease and its occurrence needs multiple genetic and environmental risk factors. Additional genetic studies on other polymorphisms in PTPN22 and possible other loci are needed for a detailed analysis concerning a role of the genetic background in CU pathogenesis.

References

- ▶ 1 Brzoza Z, Kasperska-Zajac A, Badura-Brzoza K, Matysiakiewicz J, Hese RT, Rogala B: Decline in dehydroepiandrosterone sulfate observed in chronic urticaria is associated with psychological distress. *Psychosom Med* 2008;70:723–728.
- ▶ 2 Kaplan AP: Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004;114:465–474.
- ▶ 3 Brzoza Z, Kasperska-Zajac A, Rogala B: Serum prolactin concentration and its relationship with dehydroepiandrosterone sulfate concentration in chronic urticaria patients with positive and negative response to autologous serum skin test. *Allergy* 2007;62:566–567.
- ▶ 4 Kasperska-Zajac A, Brzoza Z, Rogala B: Lower serum concentration of dehydroepiandrosterone sulphate in patients suffering from chronic idiopathic urticaria. *Allergy* 2006;61:1489–1490.
- ▶ 5 Sabroe RA, Fiebiger E, Francis DM, et al: Classification of anti-Fcεpsilon and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002;110:492–499.
- ▶ 6 Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE: EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy* 2009;64:1256–1268.
- ▶ 7 O'Donnell BF, O'Neill CM, Francis DM, et al: Human leucocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol* 1999;140:853–858.
- ▶ 8 Levy Y, Segal N, Weintrob N, Danon YL: Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003;88:517–519.
- ▶ 9 Leznoff A, Josse RG, Denburgh J, Dolovich J: Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983;119:636–640.
- ▶ 10 Lanigan SW, Short P, Moulton P: The association of chronic urticaria and thyroid autoimmunity. *Clin Exp Dermatol* 1987;12:335–338.
- ▶ 11 Leznoff A, Sussman GL: Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989;84:66–71.
- ▶ 12 Henderson CA, Hight AS: Urticaria associated with thyrotoxicosis. *Clin Exp Dermatol* 1995;20:173–174.
- ▶ 13 Turktaş I, Gokcora N, Demirsoy S, Cakir N, Onal E: The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol* 1997;36:187–190.
- ▶ 14 Kikuchi Y, Fann T, Kaplan AP: Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol* 2003;112:218.
- ▶ 15 Asero R, Lorini M, Tedeschi A: Association of chronic urticaria with thyroid autoimmunity and Raynaud phenomenon with antientomere antibodies. *J Allergy Clin Immunol* 2003;111:1129–1130.
- ▶ 16 Ryhal B, DeMera RS, Shoenfeld Y, Peter JB, Gershwin ME: Are autoantibodies present in patients with subacute and chronic urticaria? *J Invest Allergol Clin Immunol* 2001;11:16–20.
- ▶ 17 Grattan CEH, D'Cruz DP, Francis DM, Whiston C, Hughes GRV, Greaves MW: Antiendothelial cell antibodies in chronic urticaria. *Clin Exp Rheumatol* 1995;13:272–273.
- ▶ 18 Baranzini S: The genetics of autoimmune diseases: a networked perspective. *Curr Opin Immunol* 2009;21:596–605.
- ▶ 19 Hewagama A, Richardson B: The genetics and epigenetics of autoimmune diseases. *J Autoimmunity* 2009;33:3–11.
- ▶ 20 Cloutier JF, Veillette A: Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and phosphatase. *J Exp Med* 1999;189:111–121.
- ▶ 21 Gyorloff-Wingren A, Saxena M, Williams S, Hammi D, Mustelin T: Characterization of TCR-induced receptor-proximal signaling events negatively regulated by the protein tyrosine phosphatase PEP. *Eur J Immunol* 1999;29:3845–3854.
- ▶ 22 Begovich AB, Carlton VE, Honigberg A, et al: A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet* 2004;75:330–337.
- ▶ 23 Bottini N, Musumeci L, Alonso A, et al: A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nat Genet* 2004;36:337–338.
- ▶ 24 Kyogoku C, Langfeld CD, Ortman WA, et al: Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am J Hum Genet* 2004;75:504–507.
- ▶ 25 Velaga MR, Wilson V, Jennings CE, et al: The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. *J Clin Endocrinol Metab* 2004;89:5862–5865.
- ▶ 26 Criswell LA, Pfeiffer KA, Lum RF, et al: Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am J Hum Genet* 2005;76:561–571.
- ▶ 27 Brzoza Z, Grzeszczak W, Trautsohl W, Moczulski D: Protein tyrosine phosphatase-22 (PTPN-22) polymorphism in the pathogenesis of chronic urticaria. *Allergy* 2011;66:1392–1393.
- ▶ 28 Carlton VE, Hu X, Chokkalingam AP, Schrodi SJ, Brandon R, Alexander HC, Chang M, Catanese JJ, Leong DU, Ardlie KG, Kastner DL, Seldin MF, Criswell LA, Gergersen PK, Beasley E, Thomson G, Amos CI, Begovich AB: PTPN22 genetic variation: evidence for multiple variants associated with rheumatoid arthritis. *Am J Hum Genet* 2005;77:567–581.
- ▶ 29 Chung SA, Criswell LA: PTPN22: its role in SLE and autoimmunity. *Autoimmunity* 2007;40:582–590.
- ▶ 30 Kawasaki E, Awata T, Ikegami H, et al: Systematic search for single nucleotide polymorphisms in a lymphoid tyrosine phosphatase gene (PTPN22): association between a promoter polymorphism and type 1 diabetes in Asian populations. *Am J Med Genet A* 2006;140:586–593.

Acknowledgement

This study was supported by a research grant from the Medical University of Silesia.

Disclosure Statement

The authors have no conflict of interest to declare.

- ▶ 31 Huang JJ, Qiu YR, Li HX, Sun DH, Yang J, Yang CL: A PTPN22 promoter polymorphism -1123G>C is associated with RA pathogenesis in Chinese. *Rheumatol Int* 2012;32:767–771.
- ▶ 32 Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M: How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;63:777–780.
- ▶ 33 Zuberbier T, Asero R, Bindslev-Jensen C, et al: EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;64:1417–1426.
- ▶ 34 Fiebiger E, Hammerschmid F, Stingl G, Maurer D: Anti-FcεRIα autoantibodies in autoimmune-mediated disorders: identification of a structure-function relationship. *J Clin Invest* 1998;101:243–251.
- ▶ 35 Marone G, Spadaro G, Palumbo C, Condorelli G: The anti-IgE/anti-FcεRIα network in allergic and autoimmune diseases. *Clin Exp Allergy* 1999;29:17–27.
- ▶ 36 Gruber BL, Kaufman LD, Marchese MJ, Roth W, Kaplan AP: Anti-IgE autoantibodies in systemic lupus erythematosus. Prevalence and biologic activity. *Arthritis Rheum* 1988;31:1000–1006.
- ▶ 37 Tomer Y, Davies TF: Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. *Endocr Rev* 2003;24:694–717.
- ▶ 38 Ban Y, Tomer Y: Susceptibility genes in thyroid autoimmunity. *Clin Dev Immunol* 2005;12:47–58.
- ▶ 39 Simmonds MJ, Gough SC: Unravelling the genetic complexity of autoimmune thyroid disease: HLA, CTLA-4 and beyond. *Clin Exp Immunol* 2004;136:1–10.
- ▶ 40 Tomer Y, Ban Y, Concepcion E, Barbesino G, Villanueva R, Greenberg DA, Davies TF: Common and unique susceptibility loci in Graves and Hashimoto diseases: results of whole-genome screening in a data set of 102 multiplex families. *Am J Hum Genet* 2003;73:736–747.
- ▶ 41 Majorczyk E, Jasek M, Płoski R, et al: Association of PTPN22 single nucleotide polymorphism with rheumatoid arthritis but not with allergic asthma. *Eur J Hum Genet* 2007;15:1043–1048.
- ▶ 42 Ichimura M, Kaku H, Fukutani T, Koga H, Mukai T, Miyake I, Yamada K, Koda Y, Hiromatsu Y: Associations of protein tyrosine phosphatase nonreceptor 22 (PTPN22) gene polymorphisms with susceptibility to Grave's disease in a Japanese population. *Thyroid* 2008;18:625–630.
- ▶ 43 Onengut-Gumuscu S, Buckner JH, Concannon P: A haplotype-based analysis of the PTPN22 locus in type 1 diabetes. *Diabetes* 2006;55:2883–2889.
- ▶ 44 Cinek O, Hradsky O, Ahmedov G, Slavcev A, Kolouskova S, Kulich M, Sumnik Z: No independent role of the -1123 G>C and +2740 A>G variants in the association of PTPN22 with type 1 diabetes and juvenile idiopathic arthritis in two Caucasian populations. *Diabetes Res Clin Pract* 2007;76:297–303.