ORIGINAL ARTICLE

A Polymorphism in *ORMDL3* Is Associated Not Only With Asthma Without Rhinitis but Also With Chronic Obstructive Pulmonary Disease

M Balantič,[1] M Rijavec,[1] M Fležar,[1] T Camlek,[2] I Hudoklin,[3] M Košnik,[1] P Korošec,[1] S Šuškovič[1]

[1]University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
[2]Private practice for Respiratory Diseases and Diabetology, Škofja Loka, Slovenia
[3]Private practice for Respiratory and Allergic Diseases, Trebnje, Slovenia

Abstract

Background: Asthma is a heterogeneous disease, and asthmatic patients without rhinitis more commonly have fixed airway obstruction, a feature that is also typical of chronic obstructive pulmonary disease (COPD). The Dutch hypothesis suggests that both COPD and asthma have common genetic risk factors. The purpose of this study was to assess the association between the polymorphism rs4795405 in the known asthma candidate gene *ORMDL3* and asthma with and without rhinitis. We also analyzed COPD in order to investigate whether, in addition to a clinical overlap, there might also be a genetic overlap between COPD and asthma.
Methods: The population of this genetic association study comprised 493 Slovenian adults, distributed as follows: 131 patients with asthma (59 had asthma with rhinitis and 72 asthma without rhinitis), 59 patients with rhinitis only, 133 patients with COPD, and 170 controls. Genotypes for rs4795405 were determined using the TaqMan genotyping assay.
Results: rs4795405 was specifically associated with asthma without rhinitis. Assuming a recessive genetic model, we found the CC genotype in 26% of healthy controls, in 24% of patients with asthma with rhinitis (*P*=.862), and in 44% of patients with asthma without rhinitis (*P*=.006). Polymorphism rs4795405 was also associated with COPD, for which the CC genotype was found in 37% of cases (*P*=.045).
Conclusions: rs4795405 was strongly associated with asthma without rhinitis, a subtype of asthma for which a higher degree of airway obstruction was found. These results show the importance of analyzing different asthma phenotypes in genetic association studies. We also observed a genetic overlap between COPD and asthma without rhinitis.

Key words: Asthma without rhinitis. COPD. Polymorphism. *ORMDL3*.

Resumen

Antecedentes: El asma es una enfermedad heterogénea, y los pacientes en los que no se asocia a rinitis tienen una obstrucción mayor, hecho que es tambien típico del EPOC. La hipótesis holandesa sugiere un riesgo genético común en ambas patologías.
Objetivo: El propósito de este estudio fue analizar la posible asociación entre rs4795405 en el conocido gen ORMDL3, candidato de asma, y el asma con o sin rinitis. Posteriormente analizamos dichos genes en pacientes con EPOC para estudiar las posibles similitudes genéticas entre EPOC y asma.
Métodos: Para ello estudiamos 493 sujetos eslovenos adultos, 131 de ellos con asma (de los cuales 59 tenían asma y rinitis y 72 asma sin rinitis), 59 rinitis, 133 EPOC y 170 controles sanos.
En todos ellos se determinaron los genotipos para rs4795405 mediante un ensayo TaqMan.
Resultados: En los resultado obtenidos encontramos un polimorfismo de rs4795405 asociado con asma sin rinitis. Asumiendo un modelo genético recesivo encontramos el genotipo CC en un 26% de los controles, con una similar proporción en el asma con rinitis (24%, p=0.862) y un incremento de incidencia del CC en asma sin rinitis (44%, p=0.006).
El polimorfismo rs4795405 estaba también asociado a EPOC en los cuales se encontró el genotipo CC en un 37% (p = 0.045).
Conclusiones: En conclusión, el polimorfismo rs4795405 se asocia fuertemente con asma sin rinitis, un tipo de asma en el cual se encuentra un mayor grado de obstrucción bronquial.
Este estudio demuestra la importancia de analizar los diferentes fenotipos del asma en estudios de asociación genética. Además encontramos una superposición genética entre asma sin rinitis y EPOC.

Palabras clave: Asma sin rhinitis. Enfermedad pulmonar obstructiva crónica (EPOC). Polimorfismo. ORMDL3.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are complex obstructive lung diseases influenced by genetic and environmental factors [1,2]. In the last few years, a precise definition of asthma phenotypes has become increasingly important in the study of the genetic architecture and disease triggers of these phenotypes. Asthma frequently coexists with rhinitis, which is present in 80% of asthma patients [3], and thus supports the concept of "one airway, one disease" [4]. However, pathophysiology differs between asthma with rhinitis and asthma without rhinitis. Asthma patients without rhinitis are more likely to have a higher degree of airway obstruction [5], lower eosinophil counts in induced sputum samples [6-8], and, often, more severe asthma [9]. Asthma with or without rhinitis may thus represent 2 manifestations of airway disease. About 13% to 43% of COPD patients report a history of asthma [10,11], but only 8% of asthma patients report a history of COPD [11]. There are various theories about the origins of asthma and COPD. The British hypothesis posits that asthma and COPD are distinct diseases and that each develops via a unique mechanism, whereas the Dutch hypothesis supports the idea that asthma and COPD are distinct expressions of a single disease, which is affected by various environmental and epigenetic factors with a common genetic background. Consequently, asthma is most often diagnosed in childhood or adolescence, while COPD is diagnosed later in life [12]. Genetic research can benefit our understanding of their common or distinct pathogenesis.

ORM1-like 3 (*S cerevisiae*) (*ORMDL3*) is one of the most extensively studied genes in asthma and has been shown to be a candidate gene for asthma in a number of studies [13-16], conducted mainly among children. However, few studies examine the association between *ORMDL3* and asthma in adults [17,18] and none has investigated the association between polymorphisms in *ORMDL3* and COPD. Various asthma variables, such as exposure to tobacco smoke [19], early respiratory infections [20], and disease severity [21], have been analyzed to examine the association with polymorphisms in 17q21. Furthermore, in our previous work on children, we found the polymorphism rs4795405 to be associated with asthma without rhinitis but not asthma with rhinitis [16]. These (usually smaller) association studies revealed distinct asthma phenotypes and environmental effects on the association with asthma candidate genes. In addition, they served to offset the disadvantage of larger genome-wide association studies by representing more complex disease affected by comorbidities or environmental factors. Rhinitis usually precedes asthma or occurs in parallel with it [9], although different clinical phenotypes of asthma with or without rhinitis raise the question of origin and the impact of one disease on the other. Asthma patients without rhinitis and COPD patients have a high degree of airway obstruction [5,22]; therefore, early diagnosis and treatment is crucial if airway remodeling is to be limited and clinical outcome improved.

ORMDL3 belongs to a highly conserved protein family, which is anchored as transmembrane proteins in the endoplasmic reticulum [23]. The known biological function of *ORMDL3* involves regulation of Ca^{2+} uptake from cytosol to the endoplasmic reticulum. In the case of ORMDL3 overexpression, sarcoendoplasmic reticulum Ca^{2+} pump activity is reduced, thus leading to imbalances in Ca^{2+} levels and an unfolded protein response resulting in inflammation [24]. *ORMDL3* is also involved in sphingolipid metabolism [25]. Bioactive sphingolipid metabolites such as sphingosine 1 phosphate (S1P) regulate diverse cellular processes that are important for inflammation and immune responses. Changes in S1P concentrations at tissue-specific sites and in the blood have been noted in asthma [26], yet the exact role of *ORMDL3* in asthma is not known. We analyzed the polymorphism rs4795405 C>T, which is located in the intragenic region near *ORMDL3*. Although rs4795405 is not located directly in *ORMDL3*, it is often referred to as an *ORMDL3* polymorphism because it is associated with *ORMDL3* expression [13].

The purpose of this study was to investigate the association between rs4795405 in *ORMDL3* and asthma in the adult Slovenian population and to study whether there is a difference in genotype or allele frequency in asthma patients with and without rhinitis. Our assessment is based on differences in the patient's condition, such as the degree of airway obstruction and asthma severity. Furthermore, because asthma and COPD share several clinical symptoms, we analyzed the association between rs4795405 and COPD in order to investigate potential genetic links between asthma and COPD.

Materials and Methods

Study Participants

The study population comprised 493 unrelated Slovenian adults: 131 patients with asthma (59 with concurrent rhinitis

Table 1. Characteristics of Patients and Healthy Controls

	Asthma	Asthma Without Rhinitis	Asthma With Rhinitis	Rhinitis	COPD	Healthy Controls
N	131	72	59	59	133	170
Age, y, mean (SD)	50.2 (15.1)	51.0 (14.5)	49.1 (15.9)	47.6 (14.0)	63.6 (8.1)	48.0 (13.1)
Male, %	42.7	43.1	42.4	47.5	76.7	45.3
Smoking, %	10.8	13.9	6.9	16.7	40[a]	NA
BMI, mean (SD)	28.6 (5.2)	28.9 (5.0)	28.4 (5.4)	27.0 (4.0)	26.6 (4.9)	NA

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; NA, data not available.
[a]The remaining 60% of COPD patients are ex-smokers.

and 72 without rhinitis); 59 patients with rhinitis only; and 133 patients with COPD. Rhinitis, asthma, and COPD were defined according to the following guidelines: Allergic Rhinitis and its Impact on Asthma [27], Global Initiative for Asthma [28], and Global Initiative for Chronic Obstructive Lung Disease [29]. The control group consisted of 170 healthy individuals with no prior or currently established diagnosis of asthma or COPD. The characteristics of the study participants are presented in Table 1. Participants were recruited from various hospitals and are thus representative of the general Slovenian population. The study was approved by the National Medical Ethics Committee, and all participants gave their written informed consent.

Isolation of DNA and Genotyping of the Single-Nucleotide Polymorphism

Genomic DNA was extracted either from EDTA-containing whole blood samples or buccal swab samples from patients and healthy controls using the QIAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer's instructions. The genotypes of the single-nucleotide polymorphism (SNP) analyzed were determined using the 5-nuclease allelic discrimination assay in a 96-well format. rs4795405-specific primers and probes were purchased from Applied Biosystems. Allelic discrimination assays were performed in duplicate in 10-μL reaction volumes using approximately 10 ng of DNA as a template, TaqMan Universal PCR Master Mix II with UNG, and the predesigned SNP genotyping assay provided by Applied Biosystems. The temperature conditions for the polymerase chain reaction (PCR) were set at 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 1 minute. Genotyping of the amplified PCR products was based on the differences in VIC and FAM fluorescent levels using the ABI PRISM 7500 sequence detection system (Applied Biosystems) and 7500/7500 Fast Real-Time PCR v2.0 (Applied Biosystems).

Statistical Analysis

Genotype and allele frequencies were compared using the Fisher exact test based on 2×2 contingency tables and GraphPad Prism version 5.0 for Windows (GraphPad Software). Odds ratios (OR) with 95% confidence intervals (95%CI) were also calculated using GraphPad Prism. Deviation from the Hardy–Weinberg equilibrium was examined with the χ^2 test. Statistical significance was set at $P<.05$.

Results

The genotyping success rate was 100%, both for DNA isolated from blood and for DNA from buccal swabs. The genotype and allele frequencies and the results of the genotype association analysis of rs4795405 for patients and controls are presented in Table 2. The genotype distributions of rs4795405 were in Hardy–Weinberg equilibrium. The C allele in rs4795405 was associated with a significantly increased risk of asthma. The C allele was more frequent in asthma patients than in healthy controls (59% vs 49%; $P=.017$;

Table 2. Genotypes and Alleles of the *ORMDL3* Polymorphism rs4795405 in the Study Population

rs4795405 (*ORMDL3*)	No. (%)			Significant Associations	No. (%)		Significant Associations
	CC	CT	TT	CC vs CT + TT	C	T	C vs T
Asthma	46 (35)	63 (48)	22 (17)	NS	155 (59)	107 (41)	vs healthy $P=.017$
Asthma without rhinitis	32 (44)	30 (42)	10 (14)	vs healthy $P=.006$ vs asthma with rhinitis $P=.017$	94 (65)	50 (35)	vs healthy $P=.001$ vs asthma with rhinitis $P=.032$
Asthma with rhinitis	14 (24)	33 (56)	12 (20)	vs asthma without rhinitis $P=.017$	61 (52)	57 (48)	vs asthma without rhinitis $P=.032$ vs COPD $P=.044$
Healthy controls	44 (26)	79 (46)	47 (27)	vs asthma without rhinitis $P=.006$ vs COPD $P=.045$	167 (49)	173 (51)	vs asthma $P=.017$ vs asthma without rhinitis $P=.001$ vs COPD $P=.001$
Rhinitis	19 (32)	27 (46)	13 (22)	NS	65 (55)	53 (45)	NS
COPD	49 (37)	69 (52)	15 (11)	vs healthy $P=.045$	167 (63)	99 (37)	vs healthy $P=.001$ vs asthma with rhinitis $P=.044$

Abbreviations: COPD, chronic obstructive pulmonary disease; NS, nonsignificant.

OR, 1.50; 95%CI, 1.08-2.08). Furthermore, the C allele was significantly more frequent in asthma patients without rhinitis than in asthma patients with rhinitis (65% vs 52%; *P*=.032; OR, 1.76; 95%CI, 1.07-2.89) and healthy controls (65% vs 50%; *P*=.001; OR, 1.95; 95%CI, 1.30-2.92). The differences were even more evident when a recessive genetic model was used. The risk genotype CC was significantly more frequent in asthma patients without rhinitis than in asthma patients with rhinitis (44% vs 24%; *P*=.017; OR, 2.57; 95%CI, 1.20-5.49) and healthy controls (44% vs 26%; *P*=.006; OR, 2.29; 95%CI, 1.29-4.08). No differences in allele or genotype frequencies were found between asthma with or without rhinitis and rhinitis only. Finally, no differences in allele or genotype frequencies were found between patients who had asthma with rhinitis or only rhinitis and healthy controls. When COPD patients were examined, we found this disease to be associated with rs4795405. The C allele was significantly more frequent in COPD patients than in healthy controls (63% vs 49%; *P*=.001; OR, 1.75; 95%CI, 1.26-2.42); similar findings were observed for the CC genotype (37% vs 26%; *P*=.045; OR, 1.67; 95%CI, 1.02-2.73). A difference was detected in the frequency of the C allele between COPD and asthma with rhinitis (63% vs 52%; *P*=.044; OR, 1.58; 95%CI, 1.02-2.44). Interestingly, similar allele and genotype frequencies were found for asthma patients without rhinitis and COPD. To address the role of the rs4795405 genotype in specific clinical areas, we compared lung function (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]) between COPD patients with different genotypes. Patients with the CC genotype had significantly better lung function than patients with the CT and TT genotype. FEV_1 was 51% and FVC 83% in COPD patients with the CC genotype and 42% (*P*=.016) and 73% (*P*=.051) in patients with the CT and TT genotypes, respectively. A statistical analysis could not be performed owing to the lack of uniform clinical data for most of the asthma group.

Discussion

Asthma is a complex disease. Furthermore, it may be a manifestation of more than 1 disease entity, in which different pathways eventually lead to variable airway obstruction in a variety of phenotypes [30]. Airway obstruction is more commonly fixed in asthma patients without rhinitis than in asthma patients with rhinitis [5]. Using a case-control study design, we investigated the relationship between rs4795405, which is associated with childhood asthma risk and expression of *ORMDL3* in the adult Slovenian population [13]. In a previous study by our group, we confirmed that rs4795405 was associated with asthma risk in children and we found it to be strongly associated with asthma without rhinitis [16]. In the present study, we analyzed the adult Slovenian patients with asthma with and without rhinitis and found an association between adult asthma and rs4795405. Moreover, rs4795405 was strongly associated with asthma without rhinitis. The C allele, and especially the CC genotype, was more frequent in asthma patients without rhinitis than in asthma patients with rhinitis or healthy controls, for which similar genotype frequencies were found. These results highlight the importance of analyzing various asthma phenotypes in genetic association studies, because asthma is a complex, phenotypically heterogeneous disease and its manifestation could depend on genetic predisposition [31]. A particular genetic polymorphism could lead asthma to be mild or severe, for example [32], or, as in our study, accompanied by rhinitis or not. The association between asthma and rhinitis has previously been analyzed for rs7216389, one of the most studied polymorphisms in *ORMDL3*. However, this conferred no risk for rhinitis [33]. Although rs7216389 is in weak linkage disequilibrium with rs4795405 (r^2=0.77), we found no association with rhinitis only. The relatively large differences in risk genotype and allele frequencies between asthma with and without rhinitis found in our study and a replication of the results from a pediatric population with asthma [16] could indicate different disease mechanisms or crucial differences in these 2 asthma phenotypes.

Asthma and COPD are common chronic respiratory diseases with partially overlapping clinical symptoms and functional characteristics. Airway obstruction is present in both, with major differences in reversibility. In most asthma patients, obstruction is largely reversible, but in COPD patients it is fixed [22]. In COPD, airway obstruction is predominantly due to small airway disease and destruction of alveolar attachments; in asthma, larger, more proximal airways are usually the most affected, although small airway inflammation is observed, particularly in patients with severe asthma [34]. Evidence suggests that patients with asthma are predisposed to the development of COPD later in life [35]. Although most COPD patients have a history of smoking, only 20% to 50% of smokers actually develop COPD, thus indicating that genetic susceptibility plays an important role in the disease [22]. The genetic background that might predispose to COPD is more poorly understood than that of asthma, and, despite several similarities (airway obstruction and remodeling), both diseases have only rarely been addressed in a single genetic study. Given that patients with asthma without rhinitis have a higher degree of airway obstruction [5] and that a strong association was detected between rs4795405 and asthma without rhinitis [16], we expanded our study to include COPD patients in order to determine whether the known asthma risk polymorphism rs4795405 was also associated with COPD. This is the first study to analyze an association between polymorphisms in the asthma candidate locus 17q21 and COPD. The C allele, which is known to be a risk allele for asthma, was also more frequent in COPD patients than in healthy controls. The risk genotype and allele frequencies of COPD patients were similar to those of the group of asthma patients without rhinitis. These results suggest that, in addition to clinical overlap, there could also be a genetic overlap between COPD and some asthma phenotypes. The notion of a shared genetic background is further supported by other genes known to be associated with both diseases, such as adrenoceptor beta 2 (*ADRB2*) [36] and a disintegrin and metalloproteinase domain–containing protein 33 (*ADAM33*) [37-38]. Taking these data together, we demonstrated a potential association between rs4795405 and airway obstruction (ie, more fixed obstruction in asthma without rhinitis). However, as we do not have data on the FEV_1/FVC ratio, we were unable to measure obstruction, a limitation

that should be overcome in future studies. The finding of an association between the CC genotype and better lung function in COPD patients is at first unexpected, although it suggests that, despite being a risk factor for COPD, this genotype could be a favorable genetic factor for milder COPD with less affected lung function.

The CC genotype in rs4795405 could be a genetic marker for predicting the risk of asthma without rhinitis or COPD and it could help to guide the choice and intensity of therapy and thus improve patient outcome. Our results suggest that asthma and COPD share a genetic background, because polymorphism rs4795405 is associated with both entities. Our preliminary results indicate that a detailed genetic analysis of the 17q21 region should be performed for several asthma phenotypes, including asthma without rhinitis and COPD, in order to elucidate the existence of a shared genetic background.

Conclusion

Asthma is a complex disease, and our results show that polymorphisms could affect the manifestation of the asthma phenotype, because rs4795405 was associated with asthma without rhinitis but not with asthma with rhinitis. rs4795405 was also associated with COPD, making it a new shared genetic factor for these respiratory diseases, both of which are characterized by airway obstruction.

Funding

This research was supported by grant Nos. P3–0360 and J3–2234 from the Slovenian Research Agency.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Holloway JW, Yang IA, Holgate ST. Genetics of allergic disease. J Allergy Clin Immunol. 2010;125:S81-94.
2. Néstor A, Molfino MD. Genetics of COPD. Chest. 2004;125:1929-40.
3. Bourdin A, Gras D, Vachier I, Chanez P. Upper airway x 1: allergic rhinitis and asthma: united disease through epithelial cells. Thorax. 2009;64:999-1004.
4. Grossman J. One airway, one disease. Chest. 1997;111:11-16.
5. Jang AS, Park JS, Lee JH, Park SW, Kim DJ, Uh ST, Kim YH, Park CS. Asthma patients without rhinitis have more fixed airway obstruction than those with concurrent rhinitis. Allergy Asthma Immunol Res. 2010;2:108-13.
6. Dixon AE, Raymond DM, Suratt BT, Bourassa LM, Irvin CG. Lower airway disease in asthma patients with and without rhinitis. Lung. 2008;186:361-8.
7. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. Chest. 2006;130:429-35.
8. Celikel S, Isik SR, Demir AU, Karakaya G, Kalyoncu AF. Are chronic urticaria, analgesic intolerance and seasonal rhinitis markers of different severities and phenotypes of the asthma they accompany? Allergol Immunopathol. 2010;38:313-20.
9. Navarro A, Valero A, Juliá B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. J Investig Allergol Clin Immunol. 2008;18:233-8.
10. Hardin M, Silverman EK, Barr RG, Hansel NN, Schroeder JD, Make BJ, Crapo JD, Hersh CP. The clinical features of the overlap between COPD and asthma. Respir Res. 2011;12:127.
11. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest. 2005;128:2099-107.
12. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The Asthma-COPD Overlap Syndrome: A Common Clinical Problem in the Elderly. J Allergy (Cairo). 2011;2011:861926.
13. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, Depner M, von Berg A, Bufe A, Rietschel E, Heinzmann A, Simma B, Frischer T, Willis-Owen SA, Wong KC, Illig T, Vogelberg C, Weiland SK, von Mutius E, Abecasis GR, Farrall M, Gut IG, Lathrop GM, Cookson WO. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007;448:470-3.
14. Galanter J, Choudhry S, Eng C, Nazario S, Rodríguez-Santana JR, Casal J, Torres-Palacios A, Salas J, Chapela R, Watson HG, Meade K, LeNoir M, Rodríguez-Cintrón W, Avila PC, Burchard EG. ORMDL3 gene is associated with asthma in three ethnically diverse populations. Am J Respir Crit Care Med. 2008;177:1194-200.
15. Rogers AJ, Raby BA, Lasky-Su JA, Murphy A, Lazarus R, Klanderman BJ, Sylvia JS, Ziniti JP, Lange C, Celedón JC, Silverman EK, Weiss ST. Assessing the reproducibility of asthma candidate gene associations, using genome-wide data. Am J Respir Crit Care Med. 2009;17:1084-90.
16. Kavalar MS, Balantic M, Silar M, Kosnik M, Korosec P, Rijavec M. Association of ORMDL3, STAT6 and TBXA2R gene polymorphisms with asthma. Int J Immunogenet. 2012;39:20-5.
17. Karunas AS, Yunusbaev BB, Fedorova Y. Genome-wide association study of bronchial asthma in the Volga-Urals region of Russia. Molecular Biology. 45;6:911-20.
18. Hrdlickova B, Holla LI. Relationship between the 17q21 locus and adult asthma in a Czech population. Hum Immunol. 2011;72:921-5.
19. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, Chateigner N, Gormand F, Just J, Le Moual N, Scheinmann P, Siroux V, Vervloet D, Zelenika D, Pin I, Kauffmann F, Lathrop M, Demenais F. Effect of 17q21 variants and smoking exposure in early-onset asthma. N Engl J Med. 2008;359:1985-94.
20. Smit LA, Bouzigon E, Pin I, Siroux V, Monier F, Aschard H, Bousquet J, Gormand F, Just J, Le Moual N, Nadif R, Scheinmann P, Vervloet D, Lathrop M, Demenais F, Kauffmann F. 17q21 variants modify the association between early respiratory infections and asthma. Eur Respir J. 2010;36:57-64.
21. Binia A, Khorasani N, Bhavsar PK, Adcock I, Brightling CE, Chung KF, Cookson WOO, Moffatt MF. Chromosome 17q21 SNP and severe asthma. J Hum Genet. 2011;56:97-8.
22. Meyers DA, Larj MJ, Lange L. Genetics of asthma and COPD. Similar results for different phenotypes. Chest. 2004;126:105S-10S; discussion 159S-61S.
23. Hjelmqvist L, Tuson M, Marfany G, Herrero E, Balcells S, Gonzàlez-Duarte R. ORMDL proteins are a conserved new

family of endoplasmic reticulum membrane proteins. Genome Biol. 2002;3:1-16.
24. Cantero-Recasens G, Fandos C, Rubio-Moscardo F, Valverde MA, Vicente R. The asthma-associated ORMDL3 gene product regulates endoplasmic reticulum-mediated calcium signaling and cellular stress. Hum Mol Genet. 2010;19:111-21.
25. Breslow DK, Collins SR, Bodenmiller B, Aebersold R, Simons K, Shevchenko A, Ejsing CS, Weissman JS. Orm family proteins mediate sphingolipid homeostasis. Nature. 2010;463:1048-53.
26. Spiegel S, Milstien S. The outs and the ins of sphingosine-1-phosphate in immunity. Nat Rev Immunol. 2011;11:403-15.
27. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its Impact on Asthma (ARIA). 2007. [Accessed May 22, 2012]. Available from: www.whiar.com
28. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention NIH Pub. Updated 2006. [Accessed May 22, 2012]. Available from: www.ginasthma.org
29. Global strategy for Diagnosis, Managment and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). National Institutes of Health NHLBI. 2007. [Accessed May 22, 2012]. Available from: www.goldcopd.com
30. Mutius E. Gene-environment interactions in asthma. J Allergy Clin Immunol. 2009;123:3-11.
31. Meng JF, Rosenwasser LJ. Unraveling the genetic basis of asthma and allergic diseases. Allergy Asthma Immunol Res. 2010;2:215-27.
32. Halapi E, Gudbjartsson DF, Jonsdottir GM, Bjornsdottir US, Thorleifsson G, Helgadottir H, Williams C, Koppelman GH, Heinzmann A, Boezen HM, Jonasdottir A, Blondal T, Gudjonsson SA, Jonasdottir A, Thorlacius T, Henry AP, Altmueller J, Krueger M, Shin HD, Uh ST, Cheong HS, Jonsdottir B, Ludviksson BR, Ludviksdottir D, Gislason D, Park CS, Deichmann K, Thompson PJ, Wjst M, Hall IP, Postma DS, Gislason T, Kong A, Jonsdottir I, Thorsteinsdottir U, Stefansson K. A sequence variant on 17q21 is associated with age at onset and severity of asthma. Eur J Hum Genet. 2010;18:902-8.
33. Bisgaard H, Bønnelykke K, Sleiman PM, Brasholt M, Chawes B, Kreiner-Møller E, Stage M, Kim C, Tavendale R, Baty F, Pipper CB, Palmer CN, Hakonarsson H. ORMDL3 Associated gene variants are associated with asthma and exacerbations but not atopy in early childhood. Am J Respir Crit Care Med. 2009;179:179-85.
34. Jeffery PK. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2004,1:176-83.
35. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest. 2003;124:474-81.
36. Matheson MC, Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ. Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults. Hum Genet. 2006;51:943-51.
37. Gosman MM, Boezen HM, van Diemen CC. A disintegrin and metalloprotease 33 and chronic obstructive pulmonary disease pathophysiology. Thorax. 2007;62:242-7.
38. Jie Z, Hu Z, Bai C, Jin M. ADAM33 gene polymorphisms associate with asthma susceptibility and severity in East China han population. J Asthma. 2011;48:979-85.

Manuscript received September 21, 2012; accepted for publication November 19, 2012.

Matija Rijavec

Laboratory for Clinical Immunology
and Molecular Genetics
University Clinic of Respiratory and Allergic
Diseases Golnik
Golnik 36, 4204 (Slovenia)
Email: matija.rijavec@klinika-golnik.si

