Genetic polymorphisms in chronic obstructive pulmonary disease

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Key words: *chronic obstructive lung disease, polymorphisms, genetics.*

Summary. *Etiology of chronic obstructive pulmonary disease remains unknown but, despite some inconsistencies in reports on inflammatory cells, mediators and proteases involved in the pathogenesis of chronic obstructive pulmonary disease, genetic risk factors were proposed as a cause of susceptibility to the disease. Results of many studies suggested polygenic inheritance, with the genetic component consisting of several genes of a small effect each, rather than of single major gene. We are going to review the clinical importance of alpha-1 antitrypsin, glutathione S-transferase, microsomal epoxide hydrolase, matrix metalloproteinase, tumor necrosis factor-α, alpha-1 antichymotrypsin, alpha 2-macroglobulin, cytochrome P4501A1, heme oxygenase-1 genes polymorphisms associated with susceptibility and progression of the chronic obstructive pulmonary disease.*

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and irreversible airflow reduction in the lung airway. Tobacco smoke is the main environmental factor of the disease. Etiology of COPD remains unknown but genetic risk factors were proposed as a cause of susceptibility to the disease. Published twin studies demonstrate that physiological patterns of pulmonary function are inherited (1, 2). Moreover, familial aggregation studies supported a genetic component of COPD (3, 4). Results of segregation analysis (5, 6) suggested polygenic inheritance of the disease, with the genetic component consisting of several genes of a small effect each, rather than of single major gene.

Despite some inconsistencies in reports on inflammatory cells, mediators and proteases involved in the pathogenesis of COPD, many genetic studies were conducted in search for associations between genetic polymorphisms and susceptibility to COPD (7, 8). Genetic polymorphisms are relatively common (more than 1% chromosomes) differences in DNA sequence and result in population variability of genes variants referred as alleles (8). Some of these polymorphisms result in structural protein changes, altered gene expression or modifications of mRNA stability. Genetic polymorphisms affect the lung function, as was demonstrated for genes coding antiprotease-protease systems or xenobiotic metabolism enzymes. A review of clinical importance of several polymorphisms associated with susceptibility and progression of the COPD is presented.

Alpha-1 antitrypsin (AAT) is the main inhibitor of serum proteases. Congenital deficiency of AAT is associated with development of early emphysema and liver disease. The protein belongs to serpin family, a group of proteins inhibiting serine proteases activity (9). *AAT* gene is located within the serpin cluster, on the chromosome 14q23.1-3, in the proximity among others antiproteases genes: α_1- antichymotrypsin, corticosteroid-binding globulin and protein C inhibitor (10). The gene spans over 12kb and it is composed of 7 exons (11). The structure of AAT was thoroughly studied. It is a 52 kDa glycoprotein, build of 394 amino acids in the single polypeptide chain. The protein is inducible, like other acute phase proteins produced by liver. Normal levels of serum AAT are 150–350 mg/dL (11). Neutrophil elastase is the main target of AAT; elastase is attracted and bound by the serpin domain, subsequently, inhibited and degraded (12).

Over 90 different phenotypes of AAT have been described using protein electrophoresis (13). Among AAT variants M1, M2, M3, M4 are wild types found in 90% of the population (14). Two common mutations named S and Z reach the frequency of polymorphic alleles (10). It was demonstrated that different genotypes: ZZ, SZ, MZ, SS, MS cause average serum AAT concentration reduced to 16%, 51%, 83%, 93% and 97% of the wild-type MM genotype (15). ZZ homozygous have the most severe AAT deficiency. The frequency of ZZ genotype in population varies in range of 0.3 to 4.5%, depending on the study (16). Nevertheless, this genotype accounts only for 1–2% COPD cases. In Europe, frequency of Z allele declines from 5% in the North to 1–2% in the Southern Europe (16). The Z allele has single nucleotide substitution of guanine to adenine in the exon 5, changing glutamate acid (Glu342) to lysine (Lys342) in the polypeptide

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(17). Altered protein is resistant to enzymatic degradation and can aggregate. It accumulates in the endoplasmic reticulum of hepatocytes causing liver disease and low serum AAT concentration (18). ZZ genotype is associated with severe COPD and early death, especially in smokers (19). Heterozygous for Z allele identified by population studies presents, however, relatively mild form of lung disease (20). The association of the intermediate AAT deficiency, related to MZ genotype, with COPD is disputed. Study on MZ heterozygous in Denmark demonstrated a mild decrease in FEV1. This genotype was observed with moderately higher frequency in individuals with airway obstruction and COPD (21). It was suggested that MZ heterozygosity, together with some other predisposing factors, might contribute to the pathogenesis of COPD.

AAT allele S has adenine to thymine substitution within the exon 3 and results in glutamic acid 264 to valine exchange (22). Frequency of the S allele varies from 10% in the Southern Europe to 5% in the North, this gradient has opposite direction to allele Z frequency (16). SS and SM genotypes seem not to contribute in development of COPD (23). Compound heterozygous SZ genotype was associated with less severe airway obstruction than ZZ genotype (20, 24). In the recent Denmark study, SZ phenotype led to reduced pulmonary function and a fivefold increase of risk of airway obstruction, especially in smokers (20).

Glutathione S-transferases (GST) are a large family of enzymes participating in detoxification of endogenous and environmental xenobiotics (25). This group of enzymes catalyzes conjugation of the various electrophilic compounds, like polycyclic aromatic hydrocarbon epoxides, with reduced glutathione consisting in the second phase detoxification reaction (25, 26). These proteins function as dimeric enzymes, but recent data suggest GSTP monomer may have inhibitory impact on C-jun N-terminal kinase (27).

GST activity can be either cytosolic or cell membrane bound. Sixteen glutathione S-transferases genes (*GST*) have already been described, coding cytosolic GST. Six other genes code for cell membrane GSTs (26). GST cytosolic enzymes are divided in 8 classes: alpha (GSTA), mu (GSTM), theta (GSTT), pi (GSTP), zeta, sigma, kappa and chi (25). The classes are highly polymorphic. The different class enzymes preferentially conjugate different substrates: GSTM metabolizes catecholamines derivatives, GSTT1 utilizes oxidized lipids and DNA, GSTP1 metabolizes products of DNA oxidation (28). GSTP1 enzyme contributes for more than 90% of all GST activity (29). Polymorphism of *GSTP1*, *GSTM1* and *GSTT1* were studied extensively (26, 30).

GSTP1 has 4 different alleles: *GSTP1*A* (wild type), *GSTP1*B* (Ile105Val), *GSTP1*C* (Ile105Val and Ala114Val) and *GSTP1*D* (Ala114Val) (31). The activity of the enzyme is affected by substitution at the position 105 (32). *GSTP1*B* allele has a sevenfold higher catalytic activity for the diol epoxides of polycyclic aromatic hydrocarbons than a wild type allele (33). On the contrary, the same allele *GSTP1*B* has a threefold lower efficiency in conjugation of 1-chloro-2.4-dinitrobenzene (33). Results of some studies suggest that the Ala114Val substitution can augment the Ile105Val phenotype (34). *GSTP1* is abundantly expressed in alveoli, alveolar macrophages and respiratory bronchioles, more than *GSTM1*, while other glutathione S-transferases are not expressed in the lung (35). Japanese study showed increased prevalence of Ile105Ile genotype in COPD patients resulting the odds ratio 3.5 (36).

Mu class of GSTs is coded by 5 genes: *GSTM1, GSTM2, GSTM3, GSTM4, GSTM5*, all located on chromosome 1p13.3 (37). *GSTM1* has three different alleles: *GSTM1*0* (homozygous for deletion, no expression of the protein), *GSTM1*A* and *GSTM1*B* differing in one nucleotide within exon 7 (26, 30). The frequency of the *GSTM*0* allele in general population is 40–50% (35). Deleted allele was demonstrated to have higher frequency in the group of patients with emphysema and lung cancer (OR=2.1) (38).

Theta class of GST is represented by 2 genes: *GSTT1* and *GSTT2*, both localized on chromosome 22 (37). In the Caucasian population homozygous for a null allele (*GSTT1*0*) are found with 20% frequency (26, 30). Korean study failed to show any associations between the COPD and polymorphisms of *GSTM1* and *GSTT1* (39).

Microsomal epoxide hydrolase (mEPHX) catalyses hydrolysis of many exogenous arenes and aliphatic epoxides to water-soluble dihydrodiols (40). *mEPHX* is expressed in various cells, including bronchial epithelial cells (7). Several polymorphisms of *mEPHX* have been described (41). Two missense mutations: Tyr113His in the exon 3 and His139Arg in the exon 4 were reported to influence the activity of the enzyme (41). These polymorphisms determine phenotypes known as fast (homozygous wild allele in exon 3) and slow (homozygous wild allele of exon 4) metabolizer (41). Some studies suggested that slow metabolizer phenotype might be involved in the pathogenesis of COPD (42). The slow metabolizer phenotype of the enzyme was found to be more frequent in emphysema (22%), and in COPD patients group (19%) than in control subjects (13%) (42). A. J. Standford et al described association between *mEPHX* His^{113}/His^{139} haplotype and increased rate of decline of lung function (43).

Matrix metalloproteinases (MMP) are a large group of extracellular enzymes with proteolytic activity. The list of MMP seems to bee long and still incomplete. Currently 23 different MMP have already been cloned (44). The common feature for all MMP is the presence of two conserved motifs of their structure (44). The first one, named pro-domain, is composed of 80 amino acids containing a highly conserved sequence PRCXXPD (45). The second conserved domain confers catalytic activity (44). Most MMP have similar gene arrangement, this fact suggests a common origin of *MMP* from a duplicated ancestor gene (44). MMP can differ by specialized domains responsible for substrate specificity, recognition and interaction with other molecules (44).

Several *MMP* (*MMP-1,MMP-3, MMP-7, MMP-8, MMP-10, MMP-12, MMP-13* and *MMP-20*) are located in one cluster region of chromosome 11q21-23 (46). Other *MMP* are scattered over chromosomes 1, 8, 12, 14, 16, 20 and 22 (44). The function of MMP is not completely understood. Some of these enzymes seem to be responsible for tissue homeostasis while the others participate in inflammatory response, tumorigenesis and other diseases (44). MMP can act not only as proteinase but also as molecules involved in cell-cell and cell-matrix signaling. A pattern of MMP and their quantities differ between tissues (44). *MMP-1* and *MMP-9* expression is elevated in the lung of smoking COPD patients when compared to controls (47). A recent study on mice knockout of *MMP-12* (*MMP-12 -/-*) demonstrated the pro-inflammatory function of MMP-12. It induced inflammation by release of TNF- α from macrophages (48).

Several polymorphisms potentially affecting gene expression have been described in promoter regions of *MMP* (49, 50). In *MMP1* gene, insertion of guanine at position –1607 (1607G allele) introduces a new binding site for ETS-1 transcription factor (49). This allele was more frequent in patients with fast decline of lung function when compared to the non-decliners (51). *MMP12* allele A (A82G polymorphism) has apparently a higher affinity for the transcription factor activator protein-1 (AP-1) (52). The effect of another polymorphism of *MMP12*, Asn357Ser on the function of the protein is still discussed (51). In a recent study a complex interaction between *MMP1* G–1607G alleles and *MMP12* Asn357Ser polymorphisms was demonstrated and suggested association with the rate of lung function decline (51).

In the Caucasian population polymorphisms of *MMP1* and *MMP12* genes were involved in the pathogenesis of COPD (51, 53). In a recent Japanese study importance of *MMP-9* polymorphism (-1562C/T) was suggested in development of pulmonary emphysema. Allele -1562T was significantly more frequent in subjects with emphysema and odds ratio for this association was 2.69 (54). This risk allele had lower binding affinity for a transcriptional repressor (55).

Function of MMPs can be controlled by their inhibitors. In the gene coding tissue inhibitor of metalloproteinases-2 (*TIMP-2*) two polymorphisms (-418 G/C and +853 G/A) were studied in COPD patients (56). The frequency of +853G allele and -418C allele was significantly higher in the COPD group than in controls (57). The authors suggested that these polymorphisms were associated with the COPD by decrease of the transcription rate and destabilization of the mRNA.

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine coded by the gene on chromosome 6p, within the major histocompatibility complex cluster (56). TNF-α is a mediator of inflammation, and also plays an important role in host defense against a variety of fungal, bacterial and viral pathogens (58). Elevated drum and sputum levels of TNF-α (59, 60) were found in COPD patients. This observation suggested that genetic polymorphisms of the gene could associate with a susceptibility to COPD. The gene has several polymorphisms and these located within the promoter region can affect the gene expression. Several studies evaluated the effect of these polymorphisms on TNF-α production *in vitro* but results remained conflicting (61, 62). The best-studied polymorphisms of *TNF-α* located in the promoter region of the gene are: -308G/A; -376G/A and 238G/A (57). Another polymorphism, +489 G/A, was found in the first intron (63). Most of the association studies in COPD focused on –308 G/A polymorphism. Allele -308G was more frequent in Taiwanese (64) and Japanese (65) COPD patients than in controls. These results are in disagreement with case control studies on Italian (66), British (67) and Northern Americans patients (43). The possible difficulty in replication of the results was attributed to ethnic differences of allele frequency. In another study, homozygous for –308A allele were predisposed to worse prognosis in COPD (68). Only limited number of studies was published on other *TNF-α* polymorphisms in COPD. The +489A allele was more frequent in COPD group, especially in patients without radiological emphysema (56). Nevertheless, most of polymorphisms analyzed in the same study (-376G/A, -308G/A, -238G/A) did not associate with the disease (56). A. Churg et al in the recent study demonstrated that TNF-α was one of the most important mediators in smoke-induced inflammation, triggering a cascade of activation of vascular endothelial cell, followed by neutrophils influx and neutrophils' elastase release (69).

Alpha-1 antichymotrypsin (AACT) is a protease

inhibitor, which can also protect the lung against inflammatory mediated destruction. Only a few studies focused on *AACT* polymorphisms in COPD patients. Results of these studies were incoherent (70–72).

Between other genes studied for genetic association with COPD, vitamin D-binding protein gene is promising. Homozygous for 1F allele in exon 11 of the gene were more frequent in COPD than in controls and this result was confirmed in two different ethnic groups (73, 74).

Alpha 2-macroglobulin (A2M) is an inhibitor of many proteases. The most frequent alteration of the gene is 5bp deletion (75). Congenital deficiency of A2M, although rare, was associated with 20-30-fold increased risk for COPD (75).

The I phase reaction of the metabolism of xenobiotic consists on oxidation and is catalyzed by cytochrome oxidases. Cytochrome P4501A1 (CYP1A1) is an example of these enzymes family. The amino acid substitution Ile462Val in CYP1A1 increases the enzyme activity *in vivo* (76). Allele Val462 was more frequent in patients with centriacinar emphysema and in lung cancer, this association had odds ratio 2.5 (77).

In addition, Japanese study on a micro-satellite polymorphism in the promoter of heme oxygenase-1 gene reported an association with emphysema in smokers (78). This result was not replicated in other ethnic group.

Conclusions

The predictive value of genetic polymorphisms in susceptibility to COPD is still uncertain. Alpha-1 antitrypsin ZZ and SZ genotypes, *GSTP1* Ile105 allele, *mEPHX* slow metabolizer phenotype seem the best candidates for association with COPD. The clinical importance of other gene's polymorphisms is still under discussion as there is only limited number of studies performed or the data are not replicated. Results of research in the field support the polygenic model of the disease and the idea of relatively small impact of individual genetic alterations on pathogenesis of the disease.

Lėtinė obstrukcinė plaučių liga ir genų polimorfizmas

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Raktažodžiai: lėtinė obstrukcinė plaučių liga, polimorfizmas, genetika.

Santrauka. Lėtinės obstrukcinės plaučių ligos etiologija kol kas nėra visiškai aiški. Dar diskutuojama dėl atskirų uždegiminių ląstelių, mediatorių ir proteazių reikšmingumo šios ligos patogenezei, kai kurių genų polimorfizmas jau sietinas su padidėjusia rizika sirgti lėtine obstrukcine plaučių liga. Remiantis daugelio studijų duomenimis, tai daugiaveiksnės etiologijos liga, kur genetinis komponentas sąlygotas keleto genų veikimo, o vieno geno mutacijos ar polimorfizmas, kaip atskiras faktorius, turi sąlyginai nedidelę reikšmę. Apžvalgoje trumpai supažindinama su α-1 antitripsino, gliutation-S-transferazės, mikrosomų epoksidinės hidrolazės, matrikso metaloproteazės, tumoro nekrozės faktoriaus α, α-2 makroglobulino, hemo oksigenazės-1 genų polimorfizmu ir jo klinikine reikšme sergant lėtine obstrukcine plaučių liga.

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Received 27 August 2004, accepted 3 December 2004
Straipsnis gautas 2004 08 27, priimtas 2004 12 03