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THE PROMOTER POLYMORPHISM -1562C/T IN MATRIX METALLOPROTEINASE-9 AND COPD SEVERITY

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WINNING ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a complex heterogeneous respiratory disease. COPD is characterized by a progressive irreversible airflow limitation that is due to a loss of lung elasticity resulting from peripheral airflow obstruction (chronic bronchitis) and parenchymal destruction (emphysema). Matrix metalloproteinases (MMP) are a major group of proteases known to regulate extracellular matrix turnover. They have been suggested to be important in the process of lung diseases associated with tissue remodeling. Polymorphisms in MMPs which known to upregulate their activity may result in the degradation of a lung matrix.

A case-control study was performed to investigate the association of polymorphisms of *MMP* type *1* (-1607G/GG), *9* (-1562C/T) and *12* (-82A/G) genes with COPD and disease severity. A total of 309 COPD patients admitted to departments of respiratory medicine have been recruited in Ufa city hospitals (## 13, 21, and 22). COPD patients have been undergone a spirometry and a physical examination by a chest physician to refer the GOLD II-IV stages. The control group comprised of 305 healthy subjects without evidence of chronic diseases (Table Basic characteristic of study groups).

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MY JOB AND THE UNIT IN WHICH I WORK

I work in the Genomic Dept at the Institute of Biochemistry and Genetics, which belongs to Ufa Scientific Centre, a branch of the Russian Academy of Sciences (Ufa, Russia). The department consists of four laboratories investigating different aspects of human genetics and is well known for its work in ethnogenetics of various populations living in the multinational Volga-Ural region of Russia. The specific regional pattern of common monogenic diseases, such as cystic fibrosis, phenylketonuria, heritable neuronal musculopathies and many others, are a primary research focus of our specialists. More recently, high priority was given to the genetics of common diseases, such as chronic obstructive pulmonary disease (COPD), asthma, atherosclerosis, hypertension, schizophrenia and many others. We work in close collaboration with the Regional Center of Prenatal Diagnostic and all major city hospitals and health centres in Ufa.

MY WINNING POSTER AS PART OF MY RESEARCH

In June 2004, I received my PhD degree with my thesis entitled ''Polymorphic variants of genes coding for inflammatory mediators, antiproteases–proteases and xenobiotic biotransformation enzymes in COPD patients''. In order to complete this and continue my further research, I am now collaborating with major clinical departments of respiratory medicine in Ufa city. We have received great support for our COPD project from the head pulmonologist of Ufa, Prof. Zagidullin. With clinical support, we have started to collect blood samples from a large group of COPD patients and I have constructed a special questionnaire and have interviewed COPD patients in addition to collecting records from their clinical histories. In parallel with this, I have studied the basics of genetics and learned special laboratory techniques enabling me to extract DNA and analyse genotype polymorphisms in candidate genes. To select the candidate genes, I studied the pathogenesis and immunological mechanisms of COPD. The results of my research helped to characterise region-specific prevalence of COPD and the pattern of α_1-antitrypsin deficiency mutations (types Z and S) in COPD patients and healthy subjects from the Ufa region. Furthermore, we have found that some particular coincidences of ''high/low activity'' alleles in genes coding for the xenobiotic biotransformation pathway (microsomal epoxide-hydrolase and *N*-acetyltransferase) are more prevalent among COPD patients compared with controls and/or are more prevalent among patients with severe COPD. New data have been found in relation to interleukin-10 haplotypes

TABLE 1 Basic characteristic of study groups

Characteristics	COPD	Controls
Total	309	305
Male	243 (79%)	222 (73%)
Female	61 (21%)	84 (27%)
Age (mean±SEM) yrs	61.5±12.7	56.1±8.6
FEV1 % pred	39.8±6.2	ND
Smokers	168 (55%)	152 (50%)
Nonsmokers	138 (45%)	153 (50%)
Smoking index pack-yrs	35.9±5.3	27.6±3.7

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; ND: not determined.

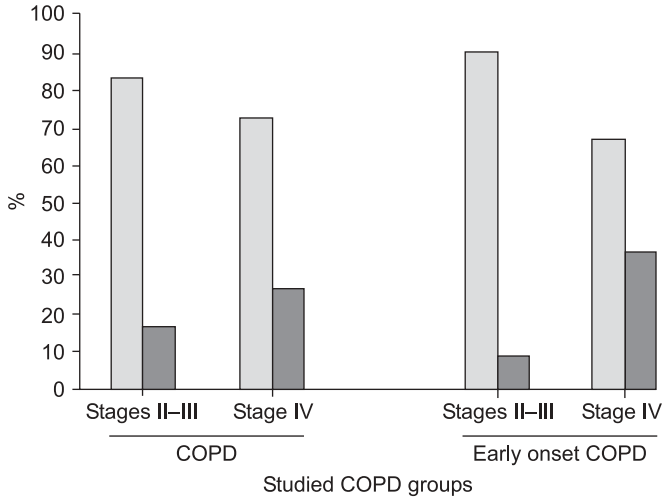

FIGURE 1. Matrix metalloproteinase 9 genotypes and chronic obstructive pulmonary disease (COPD) severity. ▫: genotype CC; ■: genotype CT+genotype TT.

and tumour necrosis factor-α and lymphotoxin-α genes systems in COPD susceptibility and severity.

MY RESEARCH AS PART OF MY WORKING GROUP/ RESEARCH TEAM

My project fits perfectly into the main research area of our group. I am a part of a team from the Laboratory of Human Ecological Genetics (headed by Prof. T.V. Victorova; Institute of Biochemistry & Genetics, Ufa Scientific Center, Russian Academy of Sciences, Ufa, Russia) and we conduct research in a field of complex diseases in which gene–environment interaction seems to play a crucial role. Ufa is a big city with a highly developed chemical and petrochemical industry. Together with smoking and alcohol consumption, occupational exposure comprises one of the powerful modifying agents of human health. Undoubtedly, common diseases, such as COPD, occupational asthma, chronic respiratory disease in children and alcoholic liver disease, studied in the laboratory, are good examples with which to investigate the influence of genes and environment on disease initiation and progression. For example, it is well known that smoking is considered to be the main risk factor for COPD development. Due to this, I have collected a comprehensive smoking history of COPD patients. However, some of the patients have also had a specific occupational exposure in their lifetime. To investigate this group further, we have recruited a separate cohort of patients with obstructive changes and total occupational exposure duration of >15 yrs [1]. We have also begun research into acute respiratory distress syndrome in pre-term children [2] to try to define a group of genes that are modifiers of lung health in children. Dr Gulnaz Korytina, a senior scientist of our research group, coordinates all projects related to respiratory medicine and investigates the genetic basis of cystic fibrosis, chronic bronchitis and relapsing pneumonia in children. A separate project is looking into genetic aspects of xenobiotic biotransformation metabolism and antioxidant defence corresponding to high/low sensitivity to occupational agents and different occupational disease susceptibility in large groups of oil-industry workers [3].

No differences have been found in a distribution of investigated matrix metalloproteinase (MMP) polymorphisms between COPD patients and controls. Further analysis of COPD patients according disease severity revealed that carriers of genotypes containing minor allele of *MMP9* (CT and TT) are more prevalent among patients with very severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV) (p=0.04; odds ratio (OR) 1.77, 95% confidence interval (CI) 0.98–3.18). Moreover, carriers of -1562T allele were more prevalent among stage IV COPD patients <55 yrs compared with patients with less severe COPD of the same age group (p=0.02; OR 4.4, CI 95% 1.13–17.25).

Our results suggest that *MMP9* could be used as genetic marker of COPD severity, particularly in patients with early onset COPD. However, further investigation of MMP gene variation is required to evaluate the association of common single nucleotide polymorphisms with COPD phenotypes.

THE IMPACT OF MY WORK ON CLINICAL OR RESEARCH PRACTICE

The completion of the human genome project and the accompanying biotechnological revolution has given rise to a new vision in the investigation of complex diseases. Genetic studies may help to provide better understanding of the origin of multifactorial diseases, such as COPD. It is generally agreed that multiple genes are likely to operate through interactions with several environmental factors. Environmental factors that contribute to disease pathogenesis may include exposure to environmental stimuli or triggers (*e.g.* allergens, occupational agents, air pollutants, tobacco smoke). The strong association of smoking with development of COPD demonstrates that those factors, in addition to genetics, play an important role in this disease. However, not everyone responds similarly to environmental stimuli, and possession of genetic disease susceptibility polymorphisms does not mean unpreventable COPD development. Furthermore, the roles of genes and environments vary across populations and, without explicit consideration of both, it is not possible to accurately identify the critical actions of either. We believe that our

research contributes to a new vision of genetics as a starting ground for future, individual patient-orientated preventive medicine.

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