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# POLYMORPHISM OF THE MICROSOMAL EPOXIDE HYDROLASE *EPHX1* GENE (RS1051740) IN FREQUENTLY ILL CHILDREN FROM AN INDUSTRIAL AREA IN SOUTHERN SIBERIA

DOI 10.25789/YMJ.2023.83.16

УДК: 575.164

**The aim of the study** was to analyze frequency of the EPHX1 gene polymorphism (rs1051740) associated with diseases of the upper airways and elevated manganese levels in biological media of children from an industrial area located in the Southern Siberia.

**Materials and methods.** We examined children aged 4-7 years who permanently lived in an industrial area in the Southern Siberia. It was a monotown with its economy dominated by a large non-ferrous metallurgy plant. The test group was made of 60 children who were often sick (more than 6 times a year) for a long time. The reference group included 39 conditionally healthy children with manganese levels in their blood being within the reference range. We identified frequency of polymorphism of the microsomal epoxide hydrolase EPHX1 gene (rs1051740) and the cytochrome C level using PCR and ELISA accordingly. The statistical significance was taken at p<0,05.

**Results and discussion**. Average manganese levels were 1,8 times significantly higher in blood of the children from the test group than in the reference one. We established statistically significant authentic differences in frequencies of the EPHX1 gene genotypes and alleles (rs1051740) between the test and reference groups (the C/C genotype was 3,2 times more frequent; the C allele, 1,5 times, p<0,05). Cytochrome C levels were 2,2 times lower in blood serum in the test group against the reference one.

**Conclusions**. The study established several peculiarities in children who often had diseases of the upper air ways (the test group). They had elevated manganese levels in their blood, higher than its safe level; the serum cytochrome C level was lower in them; they more frequently had the C/C genotype (OR=4,05, 95% CI=1,26-13,05) and the C allele (OR=1,98, 95% CI=1,09-3,60) of the EPHX1 gene (rs1051740). Many authors believe polymorphism of this gene to be a risk factor able to cause respiratory

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diseases. Deficiency of microsomal epoxide hydrolase 1, combined with the candidate gene polymorphism, disrupts detoxification, promotes accumulation of non-conjugated chemical exogenous factors (manganese), inhibits anti-oxidation and weakens the immunity. All this makes children who live in the analyzed town fall sick with respiratory diseases more frequently.

**Keywords:** xenobiotic biotransformation, the *EPHX1* gene polymorphism (rs1051740), respiratory pathology, detoxification genes, manganese contamination in biological media.

**Introduction.** At present, a lot of attention is paid to investigating contributions made by exogenous chemical factors to population incidence, children included. Occurrence and growth in environmental diseases, including respiratory ones, depend on quality of ambient air and levels of pollution in it [8]. Ambient air in industrial regions located in the Southern Siberia tends to be polluted with a wide range of harmful chemicals [3,11]. Manganese is a frequent component in emissions from non-ferrous metallurgy plants; its aerosols primarily target the respiratory organs [7]. Manganese plays an important role in many enzymatic processes in the body but if it is introduced through inhalation in excessive quantities, it can produce cumulative toxic effects [10].

An issue regarding interactions between genetic and environmental factors is no less relevant. Individual reactions to the same environmental exposures may vary significantly between keeping good health and falling sick. Therefore, it is necessary to identify certain indicators for assessing risks of various diseases, respiratory ones included. The lungs are protected from inhaled toxic chemicals and reactive oxygen species mostly by genes and enzymes that belong to the xenobiotic transformation system. The microsomal epoxide hydrolase *EPHX1* gene is located on the chromosome 1 (1q42.1). Its polymorphism rs1051740 leads to tyrosine being replaced with hystidine in the 113 location (Tyr113His) thereby reducing activity of the enzyme by 50% in C/C homozygotes and by 25% in heterozygotes. The gene plays a key role both in detoxification (with cytochrome) and development of chronic respiratory diseases; it is a protective enzyme that acts against potentially harmful small molecules penetrating the body from the environment [9,11].

**The aim of this study** was to analyze frequency of the *EPHX1* gene polymorphism (rs1051740) in children from an industrial center located in the Southern Siberia who were often sick with respiratory diseases.

**Materials and methods.** We examined children aged 4-7 years who permanently lived in a large industrial center in the Southern Siberia. It was a monotown with its economy dominated by a large non-ferrous metallurgy plant. The study was accomplished in conformity with the international standards established in the Declaration of Helsinki. The legal representatives of the examined children gave their written consent to medical examinations and tests. The test group was made of 60 children who were often sick (more than 6 times a year) for a long time. The reference group included 39 conditionally healthy children.

Manganese levels were identified in children's blood by mass spectrometry with inductively coupled plasma in accordance with the Methodical Guidelines MUK 4.1.3230-14 [MUK 4.1.3230-14 Measurement of mass concentrations of chemical elements in biological media (blood, urine) with mass spectrometry with inductively coupled plasma].

Patients' genotypes were identified by using buccal epithelium as a test material. DNA was extracted with DNK-Sorb-AM kit manufactured by the Rospotrebnadzor's Central Scientific Research Institute for Epidemiology. The Tyr113His polymorphism of the *EPHX1* gene (rs1051740) was analyzed with PCR in real time using a reagent kit provided by Syntol scientific production company and a CFX96 amplifier.

Cytochrome C levels were identified in children's blood serum by ELISA tests using a

Human Cytochrome C Platinum ELISA kit (eBioscience) and an Elx808 microplate reader.

The data were statistically analyzed with STATISTICA 6.1. The results were given as a mean value of an indicator (X), standard deviation (SD) and standard error of mean (SEM); the significance level was below 0,05. Genetic analysis of the data relied on using the Gen-Expert online calculator. The genotype distribution was tested for conformity with the Hardy – Weinberg equilibrium. We considered whether alleles or genotypes were associated with susceptibility to respiratory diseases using values of odds ratio (OR) with 95% confidence interval (95% CI). The statistical significance was taken at $p<0,05$.

**Results and discussion.** Manganese levels in blood of the children from the test group were higher than the reference ones and varied between 0,014 and 0,033 μg/cm$^3$. Manganese levels were within their reference range in the reference group where they varied between 0,006 and 0,013 μg/cm$^3$. Average manganese levels were 1,8 times higher in the test group against the reference one ($p=0,0001$) (Table 1).

We examined frequency of the Tyr113His polymorphism of the microsomal epoxide hydrolase 1 gene responsible for xenobiotic transformation and did not established any deviations from the Hardy – Weinberg equilibrium in the analyzed groups ($p=0,06$ for the test group; $p=1,00$ for the reference group).

The comparative analysis established statistically significant differences in frequency of genotypes and alleles. The C/C genotype was 3,2 times more frequent and the C allele was 1,5 times more frequent in the test group against the same indicators in the reference one ($p<0,05$). We established the following frequencies of genotypes and alleles in the children who were often sick for a long time and had elevated manganese levels in their blood: T/T, 35%; T/C, 33%; C/C, 32%; T, 52%; C, 48%. These frequencies were different in the conditionally healthy children with manganese levels in their blood within the reference range: T/T, 46%; T/C, 44%; C/C, 10%; T, 68%; and C, 32%, accordingly. The C/C genotype and the C allele of the *EPHX1* gene Tyr113His (rs1051740) created elevated risks of respiratory diseases in the test group (C/C: OR=4,05, 95% CI=1,26-13,05; C: OR=1,98, 95% CI=1,09-3,60) (Table 2).

**Table 1**

**Manganese levels in blood of the children from an industrial region in the Southern Siberia who are often sick for a long time**

| Indicator | Reference range | The test group (n=60), X±SD | The reference group (n=39), X±SD | Statistical significance, p |
|---|---|---|---|---|
| Manganese, μg/cm$^3$ | 0.006-0.014 | 0.020± 0.005 | 0.011± 0.002 | 0.0001 |

Table 2

**Frequency of the Tyr113His polymorphism of the microsomal epoxide hydrolase 1 gene in the children from an industrial region in the Southern Siberia who are often sick for a long time**

| Ген | Genotypes/ alleles | The test group (n=60) | The reference group(n=39) | OR (95% CI) | Statistical significance, p |
|---|---|---|---|---|---|
| *EPHX1* (rs1051740) | T/T | 0.35 | 0.46 | 0.63 (0.28-1.43) | 0.04 |
| | T/C | 0.33 | 0.44 | 0.65 (0.28-1.48) | |
| | C/C | 0.32 | 0.10 | 4.05 (1.26-13.05) | |
| | T | 0.52 | 0.68 | 0.50 (0.28-0.91) | 0.02 |
| | C | 0.48 | 0.32 | 1.98 (1.09-3.60) | |

Table 3

**Expression of cytochrome C protein in blood serum of the children from an industrial region in the Southern Siberia who are often sick for a long time**

| Indicator | Reference range | The test group (n=60), X±SEM | The reference group (n=39), X±SEM | Statistical significance, p |
|---|---|---|---|---|
| Cytochrome C, ng/ml | 0.1-0.5 | 0.143±0.012 | 0.316±0.067 | 0.004 |

Cytochrome C is a protein that activates xenobiotic detoxification, participates in metabolism and cell breathing. We identified its levels in both groups and established its weaker expression in the children from the test group where tis levels were 2,2 times lower against the reference group (0,143±0,012 ng/ml; p=0,004) (Table 3).

Respiratory diseases are a vital challenge for contemporary healthcare since they occupy a leading rank place in incidence, especially among children [1,9]. Children's airways have a peculiar structure that makes them more susceptible to airborne technogenic chemicals.

Enzymes of the xenobiotic transformation system and anti-oxidant protection have a significant role in protecting the lungs from toxic environmental exposures. Roles that genes can possibly have in development of diseases are established by investigating single nucleotide polymorphisms (SNPs). It is single nucleotide polymorphisms that are responsible for new functional properties of proteins. It seems rightfully relevant to identify specific genetic markers responsible for susceptibility or resistance to respiratory pathologies as predictors of health disorders [4].

According to many studies, such markers include the microsomal epoxide hydrolase 1 gene and its polymorphisms, for example, rs1051740, which is associated with respiratory diseases such as bronchial asthma, pneumonia [2], chronic obstructive pulmonary disease (COPD) [12], bronchopulmonary dysplasia, and common respiratory diseases. Our studies give evidence that Tyr113His polymorphisms of the *EPHX1* gene (rs1051740) accompany frequent diseases of the upper airways in children from an area with heavy technogenic pollution due to elevated manganese levels in biological media.

Cytochrome C levels can be considered a marker showing apparent disorders of energy metabolism and detoxification. This protein is necessary for proper functioning of the respiratory chain. Cytochrome C is a complex protein located on the internal mitochondrial membrane; it participates in the electron transport chain, inhibits lipid peroxidation, and contributes to xenobiotic neutralization [4]. We established statistically significant differences in cytochrome levels in blood serum of the children with elevated manganese concentrations in blood against the reference group (p<0,05).

Manganese is highly capable of creating chemical complexes by binding sulfhydryl groups in glutathione and blood plasma proteins and of inducing lipid peroxidation in cellular membranes. As a result, reactive oxygen species occur and this leads to developing oxidative stress and impairs functional state of various organs. Our studies established that elevated manganese contamination in biological media caused frequent respiratory diseases in children living in an area with technogenic pollution in the Southern Siberia, with the C/C genotype and the C allele of the *EPHX1* gene (rs1051740) Tyr113His [6].

**Conclusions.** We examined children who lived in an industrial area in the Southern Siberia and were often sick with respiratory diseases; as a result, we established higher frequency of the *EPHX1* gene polymorphism (rs1051740) in them in comparison with conditionally healthy children.

The children from the test group had authentically higher frequency of the C/C genotype (OR=4,05, 95% CI=1,26-13,05) and the C allele (OR=1,98, 95% CI=1,09-3,60) of the *EPHX1* gene (rs1051740); this can be a risk factor of respiratory diseases. An association between respiratory diseases and the candidate gene SPNs was also combined with elevated manganese contamination in biological media and cytochrome C deficiency (both are pathogenetically associated with microsomal epoxide hydrolase expression) in comparison with the conditionally healthy children with manganese levels in their blood remaining within its reference range.

Therefore, identification of the *EPHX1* gene (rs1051740) polymorphism reflects a risk of frequent respiratory diseases in children living in an area with heavy technogenic pollution in the Southern Siberia. We can recommend using the Tyr113His replacement of the *EPHX1* gene (rs1051740) with the C/C genotype and the C allele as a diagnostic indicator when planning and implementing activities aimed at reducing respiratory incidence among children and at preventing severe clinical forms of respiratory diseases and pathological processes in the airways (bronchial asthma, COPD, and pneumonia).

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# ANALYSIS OF ASSOCIATIONS OF CANDIDATE GENES POLYMORPHISM WITH THE DEVELOPMENT OF KNEE OSTEOARTHRITIS IN OBESE PATIENTS

DOI 10.25789/YMJ.2023.83.17

УДК 616.728.3-007.248

**Background.** Knee Osteoarthritis (OA) is a chronic disease with multifactorial pathogenesis. Risk factors for developing knee OA include age, genetic predisposition, and obesity. The share of genetic factors in the development of the disease accounts for up to 50 %. Despite the obvious association between obesity and knee OA, studies that reveal the role of genetic factors in the development of the disease in the interaction with obesity or overweight are extremely limited. **The aim of the study:** To study the association of candidate genes polymorphic loci *GDF5* (rs143384), *NFAT5* (rs6499244), *WWP2* (rs34195470), *SBNO1* (rs1060105, rs56116847) with the development of knee OA in patients with obesity. **Materials and methods**. The sample for the study included 322 obese individuals: 255 patients with OA of the knee and 67 people in the control group. Genotyping of DNA samples from all study participants was performed using standard real-time PCR on CFX96 amplifier (USA). Associations of genetic markers with knee OA in obese patients were assessed using the odds ratio and 95 % confidence interval. **Results.** Analysis of the associations of the studied polymorphic loci with the development of knee OA in obese patients revealed significant differences only for the *GDF5* (rs143384) gene polymorphism. It was established that the frequency of the G/G genotype rs143384 in obese knee OA patients was 14.12 %, which is 1.8 times less compared to the control (25.36 %, p = 0.043, OR = 0.48). **Conclusions.** The modifying role of obesity on the nature of the rs143384 polymorphic marker *GDF5* gene associations with the developing knee OA in the population of the Russia Central Chernozem Region was shown. The G/G genotype rs143384 was found to be a protective factor in the development of knee OA in obese patients.

**Keywords:** knee osteoarthritis, *GDF5*, candidate genes, obesity.

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**Introduction.** Knee Osteoarthritis (OA) is a chronic joint disease that is accompanied by progressive softening and destruction of cartilage, the growth of new cartilage and bone material at the articular margins, as well as the formation of areas of sclerosis and cysts in the subchondral bone [2]. Knee OA or gonarthrosis is widespread due to an increase in life expectancy of the population, as well as an increase in obesity [16]. According to S. Safiri et al. (2020) the prevalence of OA of the knee and hip joints worldwide is 3754.2 per 100 thousand population [10]. The social and economic importance of OA is high. Hip and knee OA ranks 11th in terms of disability in the world and 38th in terms of the number of years lived with disability [24].

Knee OA is a chronic disease with multifactorial pathogenesis [1, 16]. The leading risk factors for the development of knee OA are age, genetic predisposition, and obesity [16]. In obese individuals, the risk of developing OA is three times higher than in individuals with normal weight [6]. It is known that in patients with knee OA, who are obese or