Investigation of Syntropic Gene Polimorffisms of Multifactorial Diseases

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**Abstract**

We investigated the prevalence of polymorphisms of 4 genes: IL4 C-589T, IL17A G-197A, IL17F His-161 Arg, CYP1A1 Ile462Val among probands with atopic pathologies - bronchial asthma and atopic dermatitis and autoimmune disorders - psoriasis (PS). Set significantly higher 27% frequency of allele T-589 gene IL4 for probands with PS. In 100% of probands 462 Val Val polymorphism of the CYP1A1 gene is absent.

**Introduction**

The presence in the genome of a huge number of general candidate genes, or syntropic genes, for many multifactorial diseases (MFD) causes the development of common biochemical and physiological disorders for them (Bochkov, 2006, Grechanina, 2011, Puzyrev, 2002). The existing results of many studies have shown the association of allelic variants of interleukin genes and of xenobiotics biotransformation system genes (BS) with pathological conditions of atopy and autoallergy (Ajjan et al., 1996, Duffin and Krueger, 2009, Ghoreschi et al., 2003, Hoffjan et al., 2004, Ingelman-Sundberg, 2004, Mariotti et al., 2008, Patrick et al., 2002). Immunological disorders in atopic diseases are expressed in the change in the ratio of populations-Th1 / Th2 aside Th-2, autoimmune - on the contrary, with the productions of cytokines the first or second type accordingly, which have an antagonistic and anti-inflammatory effect on T-cells "compete" subpopulation. Some authors (Hwang et al., 2011) emphasized the role of mixed Th-1 x Th-2 answer in the destructive processes caused by a cell-mediated and antibody dependent cytotoxicity. More recent studies describe a third line of the effector cells – Th-17 cells, which act antagonistically their cytokines to Th-1 and Th-2 cell lines by expressing cytokines IL-17 family. The most well-researched - is IL-17A, IL17F (Bettelli et al., 2007, Kolls and Linden, 2004). Biotransformation of xenobiotics and endogenous substances, carried out by enzymes of cytochrome P-450 is a powerful mechanism for protecting the body from external factors and chemical regulation of metabolic reactions. CYP1 family members characterized by wide substrate specificity and izozim spectrum, that formed on a base of polymorphism coding of their genes. Genes biotransformation enzymes considered as candidates for atopy and autoimmune pathologies, since they are involved in the metabolism of inflammatory mediators leukotrienes and prostaglandins, and also in the regulation mechanisms of oxidative stress (Honkakoski and Negishi, 2000).

**Materials and methods**

Molecular genetic studies carried out based on the Ukrainian Institute of Clinical Genetics. Analyzed polymorphisms of genes IL4 (C-589T), IL17A (G-197A), IL17F (His-161 Arg), CYP1A1 (Ile462Val) using test-systems of company NTP "Liteh" in 160 patients. The group to study formed 40 people with asthma, 40 with AD, 40 - with the PC.
The control group consisted of 40 apparently healthy patients (CG). The material for the study was samples of peripheral blood. SNP was detected in 3% agarose gel. The difference of shares was evaluated by angular transformation φ. Comparison of the distribution series conducted by χ2 test at a significance level of 0.05. The expected heterozygosity gene polymorphisms IL4, IL17A, IL17F, cytochrome P450 CYP1A1 was calculated according to published procedures [3]. The relative deviation from the expected heterozygosity observed (D) was calculated using the formula: D = (h_{obs}-h_{exp}) / h_{exp}, where h_{obs} and h_{exp} - the expected and observed heterozygosity, respectively.

**Results and Discussion**

Table 1 shows the results of analysis of the distribution of genotypes of 589 CC, 589 CT, 589 TT gene IL4. From the data it is clear that the representatives of different nosologies meet all possible genotypes (Walley and Cookson, 1996). We found that the 589 CC genotype found among representatives with a BA in 1.37 times more often than among representatives from AD, and 1.25 times more likely than representatives of fields with PS.

The greatest number of representatives (40%) with genotype 589 CT is observed in the group of patients with a diagnosis of PS. This genotype occurs in less than 1.3 times of representatives from BA. But not significantly different from the frequency of representatives from AD (p > 0.05). The genotype 589TT is most common in probands with AD, 3 times more often than among probands with BA (p <0.05) and almost 2 times - than among probands with PS (p <0.05). However, the frequency of the mutant allele was not significantly different from control (p> 0.05).

Table 1. Analysis of the polymorphic locus C-589T gene IL4

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Frequency of allele C</th>
<th>h_{obs}</th>
<th>h_{exp}</th>
<th>D</th>
<th>Genotype, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>0.80</td>
<td>0.30</td>
<td>0.32</td>
<td>-0.0625</td>
<td>26(65) 12(30) 2(5)</td>
</tr>
<tr>
<td>AD</td>
<td>0.66</td>
<td>0.38</td>
<td>0.44</td>
<td>-0.1363</td>
<td>19(47) 15(38) 6(15)</td>
</tr>
<tr>
<td>PS</td>
<td>0.73</td>
<td>0.40</td>
<td>0.39</td>
<td>0.0256</td>
<td>21(52) 16(40) 3(8)</td>
</tr>
<tr>
<td>CG</td>
<td>0.67</td>
<td>0.36</td>
<td>0.42</td>
<td>-0.1428</td>
<td>23(57) 14(35) 3(8)</td>
</tr>
</tbody>
</table>

Note: n - number of genotype, h_{obs} and h_{exp} - the expected and observed heterozygosity, respectively, D - relative deviation from the expected heterozygosity observed.

Table 2 - Results analysis of the distribution of genotypes of 462 Ile Ile, 462 Ile Val, 462 Val Val of the gene CYP1A1. The data show that the representatives of different genotype nosologies not found 462 Val Val. We found that the genotype of 462 Ile Val meets with representatives of AD and PS 2 times more often than among representatives with asthma (p<0.05). As well as indicators of genotype frequencies 462 Ile Val and 462 Ile Ile identical among probands with AD and PS. This fact may be indicative of the similarity of the pathological states in dermatological diseases (AD and PS) and their common features - the "lesser" harm from toxicity environment of the body, compared with respiratory pathology - BA. One explanation for this hypothesis may be the fact that the ingenious xenobiotic metabolizing enzymes (BCF), especially CYP1A1 takes part in the metabolism of drugs, the cytochrome P450 is responsible for the side effects of drug therapy (Ingelman-Sundberg, 2004).

Table 2. Analysis of polymorphic loci Ile-462Val gene CYP1A1

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Frequency of allele Ile</th>
<th>h_{obs}</th>
<th>h_{exp}</th>
<th>D</th>
<th>Genotype, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
<td>0.98</td>
<td>0.05</td>
<td>0.04</td>
<td>0.25</td>
<td>38(95) 36(90) 36(90)</td>
</tr>
<tr>
<td>AD</td>
<td>0.95</td>
<td>0.1</td>
<td>0.095</td>
<td>0.0526</td>
<td>2(5) 4(10) 4(10)</td>
</tr>
<tr>
<td>PS</td>
<td>0.95</td>
<td>0.1</td>
<td>0.095</td>
<td>0.0526</td>
<td>0(0) 0(0) 0(0)</td>
</tr>
<tr>
<td>CG</td>
<td>0.93</td>
<td>0.07</td>
<td>0.1</td>
<td>0.094</td>
<td>37(97) 3(7) 0(0)</td>
</tr>
</tbody>
</table>

Note: n - number of genotype, h_{obs} and h_{exp} - the expected and observed heterozygosity, respectively, D - relative deviation from the expected heterozygosity observed.

For a long time the development of PS was connected with violation of the Th1-cells and overproduction of cytokines of this cell line. BA develops when the function of Th-2 cells is changed. It is established, that IL17 is expressed in the biopsy of the skin affected PS and lung with BA, because Th-17 cells are involved in immune responses in bacterial infection and pathogenetically associated with the development of chronic inflammatory diseases. After the infectious agent gets into an organism, IL17 contacts with signaled receptor IL-17RA. This reaction causes a sharp increase of neutrophils in the infection carrier organism. White blood cells disrupts lung and provoke change in all layers of the skin. IL17A and IL17F most well-studied of it’s properties cytokines of the family IL17. We have established, that the genotype 197 AA (40%) occurs among the Kharkov population patients with PS in 1.1 times more frequently than genotype 197 GG. Genotype 161His His (89%) found in 29.6 times more frequently among representatives with BA, than genotype 161 Arg Arg (3%). That fact is confirmed by the results of research conducted on laboratory mice. The damages in gen IL17 on mice was provided smaller susceptibility to lung damage provoked by a virus infection. In addition, defective mice was recorded reduced levels of neutrophils in the lung (Stark et al., 2002., Stark et al., 2010).

**Conclusions**

Analysis of genes syntropic BA AD and PS showed:

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1. Frequency of polymorphism 589 CT IL4 is maximum for psoriasis 40% (p <0.05), so this disease can be considered a key polymorphism 589 CT;
2. 462 Val Val polymorphism of the CYP1A1 gene is not found among the studied MFD;
3. Frequency of polymorphism 197AA IL17A gene for psoriasis is 40%, which shows the genetic heterogeneity of this disease.

Prospects for further research
It is planned to investigate SNP-mutation wider range of cytokines in BA, AD and PS.

References
Bochkov NP. 2006 Clinical Genetics, Moscow, 1999.