POLYMORPHISM OF INTERLEUKIN-1β GENE AND SUSCEPTIBILITY TO CHRONIC ADENOIDITIS DEVELOPMENT AT CHILDREN OF SIBERIA

The research objective was to establish a role of polymorphism of interleukin-1β gene in the locus 3954 (rs 1143634) on the chromosome 2q13-21 as a risk factor of an adverse course of the inflammatory process at chronic adenoiditis.

The research is a part of the complex scientific subject “Translational Otorhinolaryngology” which was carried out in 2010-2012. The results of genotyping of 944 people were received. High total frequency of inheritance of mutant polymorphic allelic variants of interleukin-1β gene, including homozygous (C/C) and heterozygous (C/T) carriage is revealed at children with chronic adenoiditis. The frequency was 95.5% in sampling. At a homozygous carriage of oligonucleotide replacement of thymine for cytosine in the position 3954 of interleukin-1β gene functional activity of interleukin-1β changed its pro-inflammatory effect increased by 100%. Children of this group had a heavy current chronic adenoiditis with the frequent aggravations, complications and the interfacing diseases at high concentration in blood serum interleukin-1β (298.4±8.2) pg/ml (control − 65.43 pg/ml) (p<0.001).

Keywords: Chronic adenoiditis, gene polymorphism, Interleukin-1β

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Introduction

Chronic Adenoiditis (CA) is a chronic polyetiologic disease, the base of which is the disorder of physiological immune processes of pharyngeal tonsils. Chronic Adenoiditis is the most widely spread ENT-disease among children of preschool age of the Siberian region. Even at careful examination there is an objective difficulty of establishment of the accurate criteria indicating the process of transformation of tonsils from organs, bearing useful functions in the infection centers. The beginning and the progredient development of chronic infectious and inflammatory process depends on many exogenous and endogenous factors and is characterized by such symptoms as nasal obstruction, repeated cold, snoring during a dream, low-grade fever, appetite fall, fast fatigue.

From the medical point of view CA is a multifactorial (polygenic) disease – with genetic burden.

The disease appears because of complex interactions of genetic and environmental factors. Now we have the considerable number of data confirming that in formation of predisposition to multifactorial pathology genetic polymorphism makes a contribution. Thus the greatest interest is aroused by single nucleotide replacements or SNPs. At clinical polymorphism due to SNPs there is an incorrect expression of proteins or the enzymes participating in pathogenesis of chronic adenoiditis that causes influence of genetic polymorphism on a disease phenotype that is on the clinical polymorphism. This fact predetermines distinctions in the manifestation of the same disease (rate of advance, severity of a disease course, frequency of aggravations, resistance to standard methods of therapy and others) (Mutovin, 2001).

During the inflammatory response at primary and secondary alteration a large number of mediators of an inflammation is released: humoral and cellular. One of them is
Interleukin-1β (IL-1β). For the first time interleukin-1β was described in 1972 as a factor of activation of lymphocytes. Interleukin-1β is pro-inflammatory polypeptide cytokine and participates practically in all stages of the immune response: synthesis of proteins at an acute phase by hepatocytes, chemotaxis of polymorphonucleocytes, releasing of polymorphonucleocytes from blood and bone marrow (Kampschmidt, Upchurch, Eddington, and Pulliam, 1973). These effects caused the name - endogenic mediator of leucocytes (LEM). Early researchers also called IL-1β as endogenous pyrogen because its inducing influence on fever was shown (Beeson, 1948). Other effects associated with IL-1, are an induction of prostaglandin E2 by synovial cells and collagenase release (Jasin and Dingle, 1981). Besides, IL-1 possesses a set of immunological functions, including strengthening of production of IL-2 by T-lymphocytes and activation of B-lymphocytes and thymocytes. Being truly pleiotropic IL-1 can have toxic impact on tumors by IL-2 and interferon gamma release and also indirect antiviral action by stimulation of release of interferon by beta fibroblast (Dinarello, 1989). IL-1β role in sepsis development by strengthening of growth of virulent E.coli is recently described.

Interleukin-1β is secreting molecular form of IL-1 which has molecular weight 15 kDalton and is coded on the chromosome 2q13-21 (March et al., 1985).

Allegedly the gene of IL-1 is activated at tissue damage and at an infection. Naturally in serum low IL-1β level is found. The high IL-1β rates are observed at a number of infectious diseases and noninfectious inflammatory pathologies.

In view of universality of the process of an inflammation with natural IL-1β production it is impossible to deny a role of the disorder of this cytokine development at CA.

Moreover, genetic determination of the acquired immunological insufficiency at CA is possible due to single nucleotide variations (polymorphism) of a gene coding IL-1β synthesis. Thus relevance of studying of polymorphism of gene IL -1β is caused by search of predictive criteria of chronization of the inflammatory process at adenoiditis. The concept of the personified prevention of chronic diseases of a throat at children from a perspective of molecular and genetic researches will allow not only reduce prevalence the ENT-pathology but also to develop the program of rehabilitation of the patients. The program can be applied at the out-patient departments and at polyclinics.

The personalized determination of polymorphism of IL-1β gene will allow:
1) revealing genetic disposition to CA
2) carrying out potentiation or inhibition of IL-1β expression reasonably and effectually at minimization of their adverse effect, and to take into account patient’s characteristics
3) expanding and increasing therapeutic purposes
4) predicting the course of the chronic disease is personalized.

**Materials and methods**

The study was carried out as a part of the ENT-department research “Translational Otorhinolaryngology”. The official registration number is 01201001212. The study is also a part of the thesis work “Optimization of prevention and methods of chronic adenoiditis treatment”.

The study design was considered and approved by the Local Ethical Committee of Krasnoyarsk State Medical University named after Prof. V.F. Vino-Yasenetskyy (record № 26/2010 d.d. 24.09.2010) and by the Local Ethical Committee of State-Financed Health Institution “Regional Clinical Hospital” of Krasnoyarsk city (head doctor - E.E. Korchagin) (record № 45 d.d. 27.05.2010).

The facts from the case history concerning frequency, duration, course of disease habit, aggravations, temperature reaction, existence of complications were studied.

Chronic adenoiditis diagnosis was made on the basis of anamnesis data and clinical, epidemiological, endoscopic, radiological, immunological data.
Recruitment of patients was carried out during their outpatient care or hospital treatment at the State-Financed Health Institution “Regional Clinical Hospital” and on the base of LLC “Clinic of new technologies” (Krasnoyarsk city, Russia) where blood collection for immunoassay and molecular genetic testing were undertaken.

The IL-1β level in serum of blood was determined by a method of enzyme-linked immunosorbent assay (ELISA) with application of a peroxidase of a horse-radish as indicator enzyme on the base of the certified Regional Laboratory and Diagnostic Center of Immunochemical Methods of Research of Krasnoyarsk city (the head - A.V. Svetlakov). For this purpose the certified IL-1β test systems were used (BioChemMack Diagnostics, Russia). One type of antibodies was immobilized on the internal surfaces of the cells of the plates for microtitration. The other type of monoclonal antibodies to independent epitope of molecule of required Interlaken was in the set for research in the form of conjugate with the biotin. Indicator component was the conjugate of a peroxidase of a horse-radish with streptavidin, having very high affinity to biotin. After incubations and cleaning conjugate of peroxidase of horse-radish was added in the cells. After that we again incubated, cleaned, added substratum and measured activity of the fix peroxidase with the use of the automatic vertical spectrophotometer for microplates “Multiscan MCC,340”. The quantitative contents of cytokines in serum of blood was expressed in pg/ml. Sensitivity of a method at definition IL-1β made 0,3 pg/ml. Graphs of the dependence of the optical dense on concentration for test antigen and studied samples compared to it were plotted for a quantitative assessment of results of ELISA of cytokines. Influence of circulating factors of immune system was estimated by addition to samples with known concentration of IL-1β of physiologically significant quantities of studied factors. Cross-reactivity wasn’t revealed for any studied substance.

With additional informed consent (representatives of the patient – parents) the molecular and genetic testing was carried out for children. The testing was carried out on the base of the Interdepartmental Laboratory of Medical Genetics with the active participation of the staff of the ENT-department and the Department of Medical Genetics and Clinical Neurophysiology of the Post-Diploma Institute of Krasnoyarsk State Medical University named after Prof. V.F. Voino-Yasenetsky (rector - Prof., D.M. I.P. Artyukhov) in 2010-2011.

We investigated single nucleotide polymorphisms of a interleukin-1β gene with replacement thymine (T) on cytosine (C) in the polymorphic locus 3954 (rs1143634): the wild type of the allelic IL-1β*1 variant without the mutation (T/T), the mutant type of the allelic variant (IL-1β*2 - the single nucleotide replacement of thymine on cytosine in the position 3954 (C/T); IL-1β*3 - homozygous genotype on the high-productive mutant allele - C/C.

2 ml of the fresh venous blood was used as material for molecular and genetic research. The blood was let from the patient’s ulnar vein in aseptic conditions. The letting of venous blood was made with the usage of vacuum test tubes Green Vac-Tube (South Korea) with the additive containing 0,5M solution of ethylenediaminetetramine (EDTA, pH=8,0). To pick up deoxyribonucleic acid (DNA) we applied batches of reagents from the set “DNA,sorb,V”, made by Federal State Scientific Establishment “Central Institute for Epidemiologic Scientific Research” of Federal Service for Oversight of Consumer Protection and Welfare (Moscow city, Russia).

DNA was picked out according to the following scheme. As a sample 100 mcl of blood was taken in a patient with CA. In a sample 300 mcl of lysing reagent was added. In each test tube we added 25 mcl of resuspended sorbent universal. Then we mixed it by means of the “Fugue / Vorteks Micro Backs of FV-2400” centrifuge and left in the support for 2 min. Then we once again mixed it and left for 5 min. in vertical position for DNA sedimentation on the sorbent, then sedimented the sorbent in test tubes with the “Mini Spin plus” centrifuge (Eppendorf) at a speed of rotations of 5000 rpm during 30 sec., deleted the over sedimentary liquid from each test tube by means of the suction apparatus.
“OM-1” (Russia) with a separate tip to prevent contamination of the sample, added in each test tube 300 ml of “Solution No.1” for cleaning, mixed with the centrifuge/vorteks “Mini Spin plus” (Eppendorf), then sedimented the sorbent by centrifugation at a speed of 5000 rpm during 30 sec. Again we deleted over sedimentary liquid by means of the suction apparatus “OM-1” with application of separate tips to prevent contamination of the sample. Then in every sample we added 500 ml of “Solution No.2” for cleaning, mixed with the centrifuge/vorteks “Mini Spin plus” (Eppendorf) during 30 sec. at the speed of rotations of 10000 rpm. After this manipulation the over sedimentary liquid was deleted by means of the suction apparatus “OM-1” (Russia) with separate tips for every sample. The procedure of cleaning was repeated once more. Then we placed the test tubes with the samples into the thermostat “Thermo 24-15” (Biokom) in the upright position at 65 °C for 10 min. to dry the sorbent. After that we added in the test tubes 50 ml of TE buffer for DNA elution, mixed by means of the “Mini Spin plus” centrifuge/vorteks (Eppendorf), then placed them into the “Thermo 24-15” (Biokom) in the upright position at 65 °C for 5 min., shaking them from time to time by means of the “Mini Spin plus” centrifuge/vorteks (Eppendorf). At the final stage of picking out of DNA the test tubes were exposed to centrifugation at the speed of rotation of 12 000 rpm for 1 min. by means of the microcentrifuge. 40 ml of the over sedimentary liquid was removed by means of suction apparatus “OM-1” with application of separate tips and the over sedimentary liquid containing refined DNA was replaced into the clean test tube.

As a result of the above described process samples of high-molecular DNA of patients were obtained which at a later date were stored at -20 °C.

Genetic typing was conducted by the method based on the polymerase chain reaction (PCR) in real-time mode. A method of the analyses of PCR with the usage of oligonucleotide samples marked by fluorescent agents (TaqMan technology, Life Technologies/Applied Biosystems, USA) was applied. They were complimentary to the part of the PCR-product (TaqMan technology) - deoxyribonucleic acid of the sick child blood sample. The methods of automatic detection were applied. Genotypes were determined by the presence or lacking of the product of amplification when using two DNA probes (to two alleles of each studied polymorphisms), each of which contained a fluorescent tag and a fluorescence extinguisher. Presence of this or that polymorphisms was determined by the presence of fluorescence in the amplified mixture. Negative control was included into every experiment where a DNA matrix for the PCR was replaced in real time with the distilled water (dH₂O). The PCR was conducted in real time in the “Rotor-Gene 6000” amplifier (Corbet Life Science, Australia).

Results of genotyping of 944 people were received. Results of genotyping at sick children compared with the indicators of the levels of the interleukin-1β concentration.

The group 1 - selection of patients children with CA (N=594) was composed from representatives of both sexes, Caucasian race, the Russian nationality, living in the territory of Siberia since the birth. The average age of the children with CA, made (4,98±1,70) years.

Inclusion criteria for the study:
- children at the age of 3-10 years
- Caucasian children
- residence in the region of Siberia from birth (the territory defined for the study)
- children with chronic adenoiditis (of both sexes) diagnosed by ENT specialist, allergist, pediatrician
- CA-remission and concomitant diseases
- lack of care in the previous month
- written approval of informed consent to participate in the clinical study
- patient’s ability to perform the procedure protocol.
Exclusion criteria:
- children at the age of less than 3 years and over 10 years
- children of a different race
- strangers
- exacerbation of concomitant diseases
- acute respiratory viral infection
- use of drugs that can affect the results of the study
- violation of the procedure protocol.

Group 2 - the respondents - parents of children with CA (N=250).
Group 3 - a group of children under population control (N=100). The group is presented by clinically healthy children of the same age and race as a group of the sick children.

Statistical calculations were made by means of MS Excel 2000 and SPSS v.12.0 for Windows. Variation series for each sign were studying concerning the nature of distribution with the help of the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Approaches of descriptive statistics were used in the work. The following indices were calculated: arithmetic mean (M), standard deviation (δ), the arithmetic mean error (m), median (Me), as well as the 25 and 75 percentile (P25 and P75).

The reliability of differences between the indices of independent samples was evaluated by nonparametric Mann-Whitney test. Difference between the compared series with 95% and above confidence was considered to be reliable.

Modern requirements of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation to the presentation of the results of the statistical analysis in the papers and dissertations for the scientific degree were taken into account during statistical data processing and interpretation of the received results.

Results of the study were registered in the “Protocol of integrated ENT examination” developed in accordance with the specific objectives of the study.

Results of the study

In the study we have clearly demonstrated a statistically significant prevalence of homozygous carriers of the mutant polymorphic allele variants of gene IL-1β (genotype C/C) in children with CA compared with the group of the population control (Figure 1).

**Figure 1. The frequency of genotypes of IL-1β for the mutant polymorphic allele C 3954 in the study groups (%)**

![Graph showing the frequency of genotypes of IL-1β](image)

Note: * - The level of statistical significance when comparing with the group of population control (p < 0.05).
The fact of the family aggregation of CA (the phenomenon of accumulation of genetic load) was established in families burdened by statistically significant prevalence of the homozygous genotype C/C and by a statistically significant prevalence of mutant polymorphic allele *C in parents of the children suffering from CA.

At the same time high overall frequency of inheritance of the mutant polymorphic allele variant of the gene including homozygous (C/C) and heterozygous (C/T) carrier rate was revealed in children with CA and it amounted 95.5% of the studied sample (Figure 2).

Only 4.5% of the children in the main group had a normal genotype in the studied allele, that is, they were homozygous carriers of the wild-type polymorphic allele variant of gene IL-1β (T/T).

The mutant polymorphic allele variant of IL-1β gene led to expression of a truncated and functionally defective protein IL-1β. As a result, with the homozygous carriage of the oligonucleotide substitution of thymine (T) for cytosine (C) in position 3954 on chromosome 2q13-21 functional activity of this cytokine changed - its pro-inflammatory effect increased by 100%. Indeed, children with CA - homozygous carriers of the studied mutant allele polymorphic variant of gene IL-1β - had the most severe (with frequent severe exacerbations, complications) course of the disease in comparison with the heterozygous carriers of the mutant polymorphic allele variant and homozygous carriers of wild-type allele. Among patients with severe CA (N = 355) symptoms of clinical and endogenous intoxication were recorded in 80% of the cases (N = 284), the presence of complications such as eustachitis, secretory otitis media - in 75% of the cases (N = 266).

A characteristic feature of the group of patients was frequent acute attacks - 1 time every 2 months or more than 14 days. Children in this group had higher serum concentrations of IL-1β (298.4 ± 8.2) pg/ml (control - 65.43 pg / ml) (p < 0.001).

A course of moderate CA with recurrent exacerbations of prolonged character was personalized diagnosed when identifying the heterozygous genotype for the highly productive mutant allele C/T of gene IL-1β in polymorphic locus 3954.

In patients with moderate CA (N = 212) symptoms of clinical and endogenous intoxication were recorded in 50% of the cases (N = 106), the presence of complications...
such as eustachitis, secretory otitis media in 10% of the cases (N = 21). A characteristic feature of the group of patients was prolonged exacerbations - 1 time every 3-4 months lasting 21 days. The mutant polymorphic allele variant of gene IL-1β led to a change in the functional activity of cytokine increasing its pro-inflammatory effects by 50%. Children in this group had a moderate increase in serum concentrations of IL-1β (165.4 ± 10.3) pg/ml (control - 65.43 pg / ml) (p < 0.001).

Mild CA with favorable outcome was personalized diagnosed when identifying homozygous genotype for the low-productive “wild-type” (variant of norm) allele T/T of gene IL-1β in polymorphic locus 3954. In patients with mild CA (N=27) symptoms of clinical and endogenous intoxication and complications were not recorded. A characteristic feature of this group of patients was exacerbations - 1 time every 4-6 months lasting up to 10 days. Increased serum levels of IL-1β in children of this group composed respectively (81.4 ± 6.3) pg/ml (p < 0.001).

Our research has demonstrated not only the clinical significance of the homozygous carriage of the mutant polymorphic allele variant 3954 * C in chronic adenoiditis in children, but also from the perspective of personalized medicine importance to develop algorithms for risk stratification, which are essential for optimizing the medical check-up, the development of active secondary preventive measures, individual approach to the treatment strategy. Algorithm of risk stratification during prolonged and / or recurrent disease in children with CA is presented in Table 1.

**Table 1. Risk stratification during prolonged and / or recurrent disease in children with chronic adenoiditis**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Risk level</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 group</td>
<td>low risk</td>
<td>Children suffering from CA - homozygous carriers of the wild-type polymorphic allele variant of gene IL-1β (3954 T/T)</td>
</tr>
<tr>
<td>2 group</td>
<td>moderate</td>
<td>Children suffering from CA - heterozygous carriers of the mutant polymorphic allele variant of gene IL-1β (3954 C/T)</td>
</tr>
<tr>
<td>3 group</td>
<td>high</td>
<td>Children suffering from CA - homozygous carriers of the mutant polymorphic allele variant of gene IL-1β (3954 C/C)</td>
</tr>
</tbody>
</table>

Source: Shnayder, Terskova, and Vakhruhev, 2011.

Treatment tactics of children with CA in terms of personalized medicine should be different depending on the risk of recurrence of the disease. For example, in group 1 (low risk) - it is recommended to carry out conservative therapy of CA, regular medical check-up by an otolaryngologist 1 time a year. In group 2 (moderate risk) - the following actions are possible: both conservative and surgical treatment of CA, phased courses of the local and/or system substitutive cytokine therapy with the possibility of intranasal glucocorticosteroid therapy, interdisciplinary clinical examination of the child by the otolaryngologist and immunologist 1 time every 6 months. In group 3 (high risk) - surgical treatment in combination with conservative therapy, interdisciplinary outpatient check-up of the patient by the otolaryngologist and immunologist with frequency of 1 examination every three months both in the preoperative and the postoperative periods with phased courses of intranasal glucocorticosteroid therapy.

In the aspect of predictable risks at verification of CA in the formulation of clinical diagnosis it’s appropriate to indicate a risk group of unfavorable course of the disease, e.g.: chronic adenoids, remission, risk 1.

Moreover, a low risk (15%) of spontaneous mutation “de novo” of gene IL-1β (polymorphic allele variant 3954 * C) indicates that in the vast majority of the cases the mutant allele of this gene in children with CA has been inherited from parents who are symptomatic or asymptomatic carriers of the mutation.

This fact predetermines the need for risk stratification of inheritance of genetic predisposition to CA development in siblings (brothers and sisters of the patients we
observe), and this is also urgent for genetic consultation of families with burdened history in planning (birth) of the next child for the purpose of DNA diagnostics in the preclinical stage (during the first two years of life) and the timely development and active implementation of preventive measures to minimize the action of environmental factors that contribute to the development of this multifactorial disease in siblings in case of hetero- or homozygous carriage of the polymorphic allele variant 3954 * C of gene IL-1β. Preventive talks with parents in families with burdened history with the purpose of calculating the risk of inheriting a predisposition to CA in siblings, explanation of the clinical significance of genetic risk in planning of the next child and importance of cooperation with otorhinolaryngologists in the preclinical stage can be very useful; these measures greatly improve the efficiency of primary prevention of the disease (Table 2).

**TABLE 2. RISK STRATIFICATION OF CHRONIC ADENOIDITIS DEVELOPMENT IN PRESCHOOL CHILDREN**

<table>
<thead>
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<th>Risk group</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1 group</td>
<td>low risk</td>
<td>Clinically healthy children, homozygous carriers of the wild-type polymorphic allele variant of gene IL-1β (3954 T/T)</td>
</tr>
<tr>
<td>2 group</td>
<td>moderate</td>
<td>Clinically healthy children, heterozygous carriers of the mutant polymorphic allele variant of gene IL-1β (3954 C/T)</td>
</tr>
<tr>
<td>3 group</td>
<td>high</td>
<td>Clinically healthy children (or few symptoms), homozygous carriers of the mutant polymorphic allele variant of gene IL-1β (3954 C/C)</td>
</tr>
</tbody>
</table>

Source: Shnayder, Terskova, and Vakhrushev, 2011.

Thus, only clinically healthy children at the time of the primary examination by ENT-specialist (brothers and sisters of the child with CA) entering in group 2 (moderate risk) and group 3 (high risk) should be included into the group of observation by a specialized clinic.

This approach is particularly relevant during migration, for example, when a family of a proband moves to the regions with unfavorable climatic conditions (for example, to the Far North or areas with extreme continental climate) that causes disadaptive immune system and increases influence of unfavorable environmental factor on the clinical picture of CA in individuals with genetic predisposition.

Thus, healthy children of group 3 (high risk of CA) must have a regular medical check-up by an otolaryngologist in 100% of cases because the course of CA in homozygous carriers of the mutant polymorphic allele variant 3954 * C can be oligosymptomatic sluggish.

It is advisable to carry out a screening of ENT examination of such children at least 1 time in 6 months; endoscopy and consultations of immunologist - are reasonable.

High frequent carriage of the studied polymorphic allele variant (79%) in parents (probands) of children suffering from CA confirms the fact of mutation accumulation in the observed families (a phenomenon of accumulation of genetic load). Only 16% of the revealed mutations in gene IL-1β in this selection were sporadic mutations of “de novo” that is comparable with the average population risk of sporadic mutations emergence at multifactorial diseases in population.

The results of our research allowed us to make a conclusion that it is necessary to include children of preschool age into the risk group for CA development whose parents - the carriers of the mutant allele polymorphism of 3954 * C.

For this purpose we have developed and proposed algorithm of risk stratification of chronic adenoiditis development in families with burdened history for implementation in health system; it’s presented in Table 3.
TABLE 3. RISK STRATIFICATION OF GENETIC PREDISPOSITION TO CHRONIC ADENOIDITIS IN SIBLINGS IN THE FAMILIES WITH BURDENED HISTORY

<table>
<thead>
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<th>Risk group</th>
<th>Risk level</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 group</td>
<td>low risk</td>
<td>Siblings whose brothers and sisters are sick with CA and they are homozygous (T/T) carriers of the wild-type polymorphic allele variant 3954 * T of gene IL-1β, provided that homozygous carriage of the wild-type polymorphic allele variant (T/T) in the parents (in this case the risk is caused exclusively by spontaneous mutations). Or on condition of heterozygous carriage of the mutant polymorphic allele variant (C/T) only in one parent (mother or father) - in this case the risk of genetic carriage of the mutant allele - 50% but it may increase due to the occurrence of spontaneous mutations.</td>
</tr>
<tr>
<td>2 group</td>
<td>moderate</td>
<td>Siblings whose brothers and sisters are sick with CA and they are heterozygous (C/T) carriers of the polymorphic allele variant 3954 * C of gene IL-1β, provided that heterozygous carriage of the mutant polymorphic allele variant (C/T) in both parents - in this case the risk of genetic carriage of the mutant allele - 75% but it may increase due to the occurrence of spontaneous mutations.</td>
</tr>
<tr>
<td>3 group</td>
<td>high</td>
<td>Siblings whose brothers and sisters are sick with CA and they are homozygous (C/C) carriers of the polymorphic allele variant 3954 * C of gene IL-1β, provided that homozygous (C/C) carriage in one parent and heterozygous(C/T) carriage of the mutant polymorphic allele variant in the other parent or provided that homozygous (C/C) carriage of the mutant polymorphic allele variant in both parents - in this case the risk of genetic carriage of the mutant allele - 75-100%.</td>
</tr>
</tbody>
</table>

Source: Shnayder, Terskova, and Vakhrushev, 2011.

During the development of CA in children of group 1 it is possible to assume a typical course according to immunological age period. A type of prevention for the children of this group is preventive conversation. Children of group 2 and group 3 should be taken under medical supervision, as each subsequent child in a family with burdened history accumulates genetic load on this nosology by 6-8%.

We believe that a widespread introduction of the principles of personalized medicine into everyday clinical practice at the primary health level and specialized ENT clinics will provide not only high medical effectiveness of the proposed algorithms due to the reduce of exacerbations and cases of prolonged and / or recurrent CA in children but also high social efficiency by reducing the number of cases of coupled pathology, particularly the socially significant conductive poor hearing and labor losses by reducing a number of disability days to care for a sick child.

Currently, development of medicine and biology is changing from mass care to personalized therapy. It is a personalized approach that can cure a patient with high efficiency by correcting individual immunity disorders.

That is why integration based on systems biology of genomic technologies and study of genetic determination in ENT pathology is a basic methodological principle to achieve the ideal proclaimed by Hippocrates “treat not a disease but a patient.”

Verification of significant prognostic criteria of efficiency will make prevention and therapy predictable and highly effective.
References


