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IL1B GENE POLYMORPHISM IN CHILDREN WITH GINGIVAL RECESSION

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Abstract:
Gingival recession is a multifactorial disease. Various factors are involved in its development and progression. The main factor is currently believed to be genetic, as a result of a genetically incorporated wrong ratio of size, shape (signs of curvature) of the roots relative to the thickness of the alveolar bone of the jaw. The aim of the research was to study the association of the polymorphism -511 C / T, (rs16944) of the interleukin-1b gene (IL1B) with a predisposition to the development of gingival recession in children and conditionally healthy donors living in the territory of the city of Kazan in the Republic of Tatarstan. The study included 84 children (41 girls, 43 boys) with gum recession. The age of the examined children was from 6 to 12 years old (average age 8.12±1.06 years), and the control group consisted of 283 conditionally healthy donors not having a gum recession. DNA was isolated from buccal epithelial cells by the sorbent method, in accordance with the attached instructions for use of the «AmpliPrym DNA-Sorb-B» DNA Extraction Kit («NextBio», Russia). It was shown that in the group of children with gum recession, the SS genotype was predominantly determined (45.2%). The ST genotype in the comparison groups and with the gum recession were unequivocal (39.2% and 39.5%, respectively, of the cases). T-allele carriers were more common in the comparison group (healthy) (P = 0.089).
Key words: *gum recession, children, cytokine IL1B genes, association, genetic polymorphism.*

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INTRODUCTION:

The problems of etiology and pathogenesis of gum recession are relevant for modern dentistry. To date, gum recession is a common disease, which is progressing with increasing age of patients [1,2,3,4].

There are several theories explaining the occurrence of gingival recession, in one of which genetic factors are analyzed, as well as the influence of exogenous stimuli (orthodontic appliances, denture constructions, small mouth vestibules, crowded teeth, etc.) [2]. The priority factors for the occurrence of gum recession are the pathology of the attachment of soft tissues and dental-anomalies [1]. The main reasons for the development of gingival recession are: genetic predisposition, as a result of a genetically incorporated improper size ratio, shape (signs of curvature) of the roots relative to the thickness of the alveolar bone jaw [2, 3, 5-8]. Functional trauma, aggressive teeth cleaning, iatrogenic factors are also important [6, 9].

At the same time, the role of genetic susceptibility to the development of many dental diseases, including gingival recession, and the intensity of their progression is currently not well understood.

Currently, many authors have shown that carriers of certain alleles of some cytokine genes have an increased risk of developing periodontal diseases, a significant correlation has been found between the severity of periodontitis and the increased expression of IL1B, TNF-[10-17].

It is known that a gene is a region of chromosomal DNA consisting of exons, protein-coding regions, and introns, and segments that carry no information. The gene on both sides is limited to the regulatory regions responsible for the initiation and synthesis of RNA. The biological role of most genes is in coding information about the structure of certain proteins. According to modern concepts, individual differences of each person are due to gene polymorphisms. Genetic polymorphism - the diversity of nucleotide sequences of a gene, including its allelic forms, can be characterized as the difference in the nucleotide sequence of a DNA molecule that is observed between individuals. Mutations are changes in the nucleotide sequence, which lead to gross dysfunctions of the encoded proteins, significantly affect human vitality and are common in a population with a frequency of less than 1%. Polymorphic genes are genes manifested in a population by a variety of alleles. Genes of predisposition are mutant alleles that

are compatible with birth and life in the postnatal period, but under adverse conditions may contribute to the development of one or another disease [18]. Polymorphism inside the exon of a gene can lead to changes in the structure of the protein and disruption of its functions, and within the regulatory region of the gene - to a violation of transcription and protein synthesis.

As a result of the implementation of the project "Human Genome" (1990-2003), genes have been identified that lead to hereditary human diseases and increase the risk of developing multifactor diseases.
It is known that natural polymorphism in cytokine genes determines the individual features of the synthesis and biological activity of cytokine molecules [19]. Cytokines are a group of non-enzymatic protein hormones that are mediators of cell-cell interactions, are involved in the induction of inflammation and determine the nature of the immune response to provoking factors. Cytokines include interferons, chemokines, colony-stimulating factors, interleukins, and other endogenous mediators [20, 21]. One of the key inflammatory cytokines is interleukin-1 (IL-1), a cytokine with a broad spectrum of biological and physiological effects. IL-1 is a cytokine with fibrogenetic and pro-inflammatory properties. The most important members of the IL-1 family are IL-1-alpha, IL-1-beta and their natural inhibitor, an antagonist of IL-1 receptors (IL-1Ra) [21]. IL-1α and IL-1β are two separate gene products. [21].

The IL1B gene, encoding IL-1β, is located in the 2q13-q21 region of the 2nd chromosome and contains 22 exons, 20 of which are alternative (ie, have structural variants) and 9 introns, of which 8 are alternative. In the region of this gene, 135 single nucleotide substitutions were found.

A number of point markers of the IL1B gene were identified: -3737, -1469, -999, -511, -31, +3953, +3962, but the two studied IL1B polymorphisms are the most studied: in the 5th exon (C3953T) and the C – 511T polymorphism (replacement of cytosine nucleotide (C) with thymine (T) at position -511 of the nucleotide sequence in the promoter part [22]. In variant –511T, IL-1β production is increased, which leads to activation of local inflammatory reactions [23, 24].

Considering the high prevalence of gingival recessions in children, as well as the fact that the etiology of the educational process and the factors triggering gum recession are not well understood, it is relevant to study the polymorphism of cytokine genes involved in various body reactions and the study of molecular genetic criteria leading to gum recession.

The purpose of this study was to study the association of the polymorphism -511 C / T, (rs16944) of the interleukin-1β gene (IL1B) with a predisposition to the development of gingival recession in children and conditionally healthy donors living in Kazan, the Republic of Tatarstan.

MATERIAL AND METHODS:

84 children (41 girls, 43 boys) with gum recession were examined. The age of the examined children was from 6 to 12 years old (average age 8.12 ± 1.06 years). Patients were included in the appropriate group after establishing the diagnosis of the disease, confirmed using clinical and laboratory and instrumental methods of examination; the control group consisted of 283 conditionally healthy, not having a recession gums, donors. The groups were comparable in age and sex. All study participants were of Caucasian origin and lived in the territory of Kazan, the Republic of Tatarstan.

The criteria for inclusion in the study was the presence of a recession of the gums of I, II class according to Miller, which was determined visually and / or using an x-ray method [25].

Exclusion criteria from the study: the absence of gum recession, the presence of other periodontal diseases, patients of another ethnic group. All patients according to the history of the disease were analyzed complaints and anamnesis of the disease

Parents of all patients signed voluntary informed consent before the study. The permission of the Local Ethics Committee of Kazan State Medical University of the Ministry of Health of Russia (Minutes No. 6 of June 28, 2016) has been obtained to conduct the study.

To study the polymorphisms of the C (-511) T (rs16944) IL1B gene, genomic DNA samples isolated from buccal epithelial epithelial cells, obtained by scraping with a sterile, universal disposable probe, were used. DNA was isolated by the sorbent method, in accordance with the attached instructions for use of the AmpliPrime DNA-Sorb-B DNA Extraction Kit (NextBio, Russia). The isolated DNA was placed in a freezer and stored at t -20 ° C until the PCR was performed.

Determination of the polymorphism C (-511) T (rs16944) IL1B gene was performed by allele-specific polymerase chain reaction (PCR) using

dvuhpraymernoy system followed by restriction analysis (forward primer - TGGCATTGATCTGGTTCATC, reverse primer - GTTTAGGAATCTTCCCACTT, restriction enzyme Aval («SkyGene», Russia). PCR was carried out in a DT-96 amplifier (DNA technology, Russia) [26].

Analysis of the lengths of restriction products was carried out by electrophoretic separation in an 8% polyacrylamide gel (PAAG) followed by staining with ethidium bromide (5 μg / l) followed by visualization in transmitted ultraviolet light and documentation using the photodocumentation system using the transilluminator ETSVilberLourmat (France).

Statistical data processing was performed using the standard package GraphPadInStat. Correspondence of the distribution of genotypes in Hardy-Weinberg equilibrium samples was determined using criterion χ^2 (compared with genotypes of control groups). Differences were considered statistically significant when $p \leq 0.05$. To assess the connection with the development of gingival recession, the odds ratio (OR - oddsratio) was considered with a 95% confidence interval (95% ConfidenceInterval - 95% CI).

RESULTS AND DISCUSSION:

The results of the genetic analysis showed that in all groups of the examined children (with gum recession and in the control group) all three genotypes were identified - CC, CT, TT with different frequency of occurrence. At the first stage of the analysis, the distribution of the frequency of occurrence of alleles and genotypes of the polymorphism of the gene IL1B C (-511) T (rs16944) in patients with gum recession was established. The observed frequencies of alleles and genotypes in a sample of patients with recession gums were consistent with the Hardy-Weinberg law. When analyzing the frequency distribution of genotypes of the polymorphic locus C-511 T of the IL1B gene in the groups of individuals examined, the following data were obtained: the genotype CC - 38 (45%), CT - 33 (39%), TT - 13 (16%). Alleles n = 168 - C - 109 (65%), T - 59 (35%), which corresponds to the frequency of alleles in the European population. In the case of control, healthy patients: the genotype CC - 106 (37%), CT - 112 (39.6%), TT - 65 (23%). Alleles n = 566, C - 324 (57%), T - 242 (43%).

When comparing the distribution of IL1B C (-511) T genotypes (rs16944) in children with gingival recession and the control group, no significant difference was observed.

As a result of our study, it was found that the SS genotype was predominantly determined in the group of children with gingival recession (45.2%). The CT genotype in the comparison groups and with the gum recession were unambiguous (39.2% and 39.5%, respectively, of the cases). T-allele carriers were more common in the comparison group (healthy) (P = 0.089).

In patients with gingival recession, the frequency of the C allele and the homozygous C / C genotype of the polymorphic locus C (–511) T of the IL1B gene were higher (by 7.7% and 7.8%, respectively), and the frequency of the T allele and the T / T genotype were lower than in the control group (by 8% and 7%). The occurrence of the heterozygous genotype C / T of the polymorphic locus C (-511) T of the IL1B gene did not differ between the studied groups.

CONCLUSION:

In recent years, one of the priority areas of medicine is the search for molecular genetic markers of various diseases, allowing to form a risk group. Currently, there are no reliable markers for assessing the susceptibility of a particular patient to the development of gum recession, and for determining the prognosis of the disease, which makes it difficult to diagnose early and effective timely therapy. In this regard, interest in the study of genetic risk factors for the development of gingival recession has recently increased significantly. As genetic factors that determine the individual characteristics of the course of diseases, single nucleotide polymorphisms (single nucleotide substitution for another, or single-nucleotide polymorphisms SNPs), the most common form of genetic variation, are used to determine the prognosis of diseases [27, 28, 29]. Single nucleotides (SNPs) are more common than any other type of genetic polymorphism [29,30].

There are various sequence variants (alleles) in the genomic DNA, and, a rare allele is found in a population with a frequency of at least 1%. A large number of SNPs in the human genome is capable of providing significantly greater mapping density. Only at such a high density does it become possible, by comparing large samples of healthy and sick individuals, to identify genes involved in the manifestation of polygenic traits. This allows you to explore the molecular nature of the patient's predisposition to various diseases and to increase the effectiveness of their early diagnosis and treatment.

Thus, during the study, we found no significant differences in the frequencies of alleles and

genotypes of the IL1B gene between children with gingival recession and the comparison group. An insignificant dominance of the homozygous C / C genotype was found in the C -511 T polymorphic locus of the IL1B gene, and carriers of the T allele were less common in children with gingival recession when compared with the control group, which did not meet expectations.

In the work of Volkova V.V. et al. (2016) also showed that the IL1B C (-511) T (rs16944) gene was not associated with gingival recession [31].

The authors of the following works studied the polymorphism of the gene IL1B (C / T -511) in patients without comorbidities and compared the data with the dental status of patients. They concluded that patients with the C / T and T / T genotypes (that is, carriers of the T allele) have a greater risk of developing periodontal pathology than patients with the C / C genotype [32-34].

Findings:

Polymorphism -511 C / T in the promoter region of the IL1B gene is not associated with a predisposition to the development of gum recession in children. Further studies are needed with the expansion of samples and analysis of other gene polymorphisms to identify genetic risk factors for the development of gingival recession.

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