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# Study of Polymorphism of COL1A1 G2046T in Girls with Juvenile Dysmenorrhe Depending on the Presence of Connective Tissue Dysplasia in the Uzbek Population

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**Abstract:** ***The article studies polymorphisms of COL1A1 G2046T in girls with juvenile dysmenorrhea depending on the presence of connective tissue dysplasia in the Uzbek population. When studying the Association of the COL1A1 genotype G2046T it was found a significant increase in mutant genotype TT in the group of girls with a juvenile dysmenorrhea (JD) with connective tissue dysplasia (CTD) in comparison with practically healthy persons.***

**Keywords:** Uzbek, population, polymorphism, juvenile dysmenorrheal, connective tissue dysplasia

## 1. Introduction

Dysmenorrhea is a common pathological condition characterized by painful menstruation. From modern neurophysiological positions it is called as a menstrual pain syndrome, which is more competent, since it can be designated the whole wide range of neurovegetative, metabolic-endocrine and psycho-emotional deviations of the menstruation process, accompanied by pain in the lower abdomen [4, 5].

According to this definition, juvenile dysmenorrhea (JD) is a signal of disorders that have developed in systems that provide and control the process of rejection of the endometrium. In the event of a pathological situation in the body of a growing female body is the formation of pathological conditions of organs and tissues in the form of dysplastic manifestations from the connective tissue. A wide variety of clinical criteria for the severity of undifferentiated connective tissue dysplasia (CTD) has been established, but the features of connective tissue metabolism are still unclear. Their establishment will allow a deeper understanding of the pathogenesis of JD and create new therapeutic and preventive approaches to the treatment of painful menstruation in girls [1].

In the study of CTD, the question arises about the possible cause of changes in the connective tissue on the basis of genetic predisposition. As is known, the manifestation of a disease is often due to the combination of certain allelic variants of genes in the host genotype, polymorphisms that form a certain hereditary background, which can be implemented in the interaction of the pathological genotype with environmental factors.

To date, it has been established that the human endometrial undergoes cyclic waves of proliferation, differentiation, apoptosis and regeneration, depending on the increase and decrease in the levels of estradiol and progesterone synthesized in the ovaries. Synthesis of specific proteins of estrogen alpha receptors is determined by the gene Era (ESR1). This gene is located on chromosome 6q25. It consists of 8 exons, 7 introns and occupies more than 140 kilobases. The molecular mechanisms by which these polymorphisms affect receptor activity remain obscure. RFLP is detected in the intron, i.e. a virtually non-functional region of the gene, and since they are separated by 50 pairs of bases, are assumed to be in a strong linear coupling [2, 3].

The aim of the study was to study the polymorphism of COL1A1 G2046T in girls with juvenile dysmenorrhea depending on the presence of connective tissue dysplasia in the Uzbek population.

## 2. Material and Methods

We conducted a clinical and genetic survey of 118 girls, with the signs of the DST - 64, and without it – 54, the control group consisted of 68 healthy women with normal menstruation. The genetic study was conducted by polymerase chain reaction (PCR) using specific primers (NPF Litech, Russia) in the automatic amplifier "Rotor Geene 6000". Determination of free and bound oxyproline in urine was carried out by the method of Sharaev P. N.[4]. The data obtained in the study were statistically processed on a personal computer Pentium-IV using the software package Microsoft Office Excel-2012, including the use of built-in functions of statistical processing.

## 3. Results and Discussion

The basis for the diagnosis of dysmenorrhea was a complaint of painful menstruation. He conducted one momentary examination of the state of health to exclude organic pathology, i.e. secondary dysmenorrhea (ultrasound of the pelvic organs, smear on the flora, examination of the vertebrologist).

As presented in table 1, the analysis of the distribution of allelic variants of the gene COL1A1 G2046T showed that in the group of patients with JD, accompanied by CTD significantly higher compared with the control group of

healthy individuals, there was only a tendency to the reliability of alleles, but they did not reach the true significance.

**Table 1:** Distribution of frequencies of alleles and genotypes of COL1A1 G2046T gene in girls JD with DST in comparison with control group of healthy individuals

| Genotype | JD+CTD | | Control | | OR | χ2 | P |
|---|---|---|---|---|---|---|---|
| | n=64 | % | n=68 | % | | | |
| G | 97 | 75,78 | 114 | 83,82 | 0,60 | 2,658 | 0,1 |
| T | 31 | 24,22 | 22 | 16,18 | 1,66 | 2,658 | 0,1 |
| GG | 41 | 64,06 | 48 | 70,59 | 0,74 | 0,639 | 0,4 |
| GT | 15 | 23,44 | 18 | 26,47 | 0,85 | 0,162 | 0,6 |
| TT | 8 | 12,50 | 2 | 2,94 | 4,71 | 4,302 | 0,03 |

While a significant increase in the homozygous TT genotype was observed in the group of girls with YD and DST compared with the control group ($\chi2$= 4,302, p < 0,03, OR≥4,71). Further, in the study of the distribution of allelic variants of the gene COL1A1 G2046T in the group of patients with JD, accompanied by CDT compared with the group of girls with JD without CDT, it was found that there were no significant differences in allele frequencies in these groups (table 2).

In the next stage it was decided to analyse the distribution of frequencies of occurrence of allelic variants and genotypes of COL1A1 G2046T in a group of girls with a JD without the CTD in comparison with practically healthy persons in the population control.

**Table 2:** Distribution of frequencies of alleles and genotypes of col1a1 G2046T JD with CTD in comparison with control group with JD without CTD

| Genotype | JD+CTD | | JD without CTD | | OR | χ2 | P |
|---|---|---|---|---|---|---|---|
| | n=64 | % | n=54 | % | | | |
| G | 97 | 75,78 | 88 | 81,48 | 0,71 | 1,124 | 0,2 |
| T | 31 | 24,22 | 20 | 18,52 | 1,41 | 1,124 | 0,2 |
| GG | 41 | 64,06 | 37 | 68,52 | 0,82 | 0,26 | 0,6 |
| GT | 15 | 23,44 | 14 | 25,93 | 0,87 | 0,09 | 0,7 |
| TT | 8 | 12,50 | 3 | 5,56 | 2,43 | 1,671 | 0,2 |

As can be seen from table 3, in the course of the analysis of these groups, there was no significant difference either for allelic variants or for genotypes.

**Table 3:** The frequency distribution of alleles and genotypes of COL1A1 gene G2046T the girls with a JD without the CTD in comparison with the control group of healthy individuals

| Genotype | JD without CTD | | Control | | OR | χ2 | P |
|---|---|---|---|---|---|---|---|
| | n=54 | % | n=68 | % | | | |
| G | 88 | 66,67 | 114 | 83,82 | 0,85 | 0,23 | 0,6 |
| T | 20 | 18,52 | 22 | 16,18 | 1,18 | | |
| GG | 37 | 68,52 | 48 | 70,59 | 0,91 | 0,06 | 0,8 |
| GT | 14 | 25,93 | 18 | 26,47 | 0,97 | 0,005 | 1 |
| TT | 3 | 5,56 | 2 | 2,94 | 1,94 | 0,523 | 0,4 |

Thus, when studying the Association of the COL1A1 genotype G2046T it was found a significant increase in mutant genotype TT in the group of girls with a JD with CTD in comparison with practically healthy persons.

**Table 4:** The level of oxyproline in daily urine (μmol/day) in girls with JD, depending on the presence of CTD criteria (M±m)

| Group | The content of hydroxyproline mk/mol/day | | |
|---|---|---|---|
| | C-free | Peptide-bound | Protein-bound |
| Practically healthy, n=25 | 18,4±1,34 | 155,7±13,6 | 8,4±0,63 |
| JD without CTD | | | |
| easy, n=10 | 18,81±0,30 | 156,63±0,16 | 8,33±0,26 |
| average, n=31 | 18,42±0,27 | 155,81±0,24 | 8,32±0,23 |
| heavy, n=15 | 17,82±0,35 | 156,33±0,37 | 8,11±0,35 |
| JD with CTD | | | |
| easy, n=24 | 26,02±0,96[a,b] | 163,64±0,97[a,b] | 8,45±0,55 |
| average, n=100 | 34,54±1,07[a,b] | 167,33±0,92[a,b] | 8,20±0,63 |
| heavy, n=50 | 57,83±0,88[a,b] | 171,06±0,97[a,b] | 8,82±1,51 |

This may indicate that the single-nucleotide version of COL1A1 G2046T, plays a role in the pathogenesis of the development of JD is ACCOMPANIED by CTD. This is indirectly confirmed by the indicators of hydroxyproline (Table.4), but taking into account the fact that the increase in the level of this indicator was significant in comparison with practically healthy individuals and in comparison with a group of patients with JD without signs of CTD, allows us to assume that this polymorphism is only one of the polymorphisms involved in the pathogenesis of the pathology under study.

Based on the above it can be concluded that the occurrence of the mutant allele of the gene of estrogen receptor – alpha (single-nucleotide substitutions of guanine for adenine in rs2228480), 1.9 times higher in the group of girls with a JD with CTD than in the group JD without a CTD ($\chi2$ = 4,515; p=0.03). There was also a significant difference in the frequency of collagen type I gene polymorphism (single-nucleotide replacement of guanine with thymine in rs1800012) was found in girls with JD with CTD only in comparison with a group of healthy individuals ($\chi2$=4.71; p = 0.03).

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