

EXPANSION OF TRINUCLEOTIDE CTG REPEATS IN THE *TCF4* GENE AS A MARKER OF FUCHS' ENDOTHELIAL CORNEAL DYSTROPHY

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✧ Fuchs' endothelial corneal dystrophy (FECD) is an inherited severe and progressive disease, characterized by endothelial cell density decrease and increasing corneal edema. FECD development may be linked to expanded trinucleotide repeat, CTG, in the third intron of the *TCF4* gene. The study focuses on estimating the prevalence of expanded CTG repeat in *TCF4* gene in the Russian population, in patients with normal cornea and in patients with FECD (by applying triplet repeat PCR technique and capillary electrophoresis). 51 patients with FECD and 38 patients with normal cornea were examined. The estimation of the number of CTG triplet repeats in *TCF4* gene determination is the veracious laboratory marker of FECD.

✧ **Keywords:** Fuchs' endothelial corneal dystrophy; *TCF4*; trinucleotide repeat; CTG repeats; triplet repeats PCR.

ЭКСПАНСИЯ ТРИНУКЛЕОТИДНЫХ СТГ-ПОВТОРОВ В ГЕНЕ *TCF4* КАК МАРКЕР ЭНДОТЕЛИАЛЬНОЙ ДИСТРОФИИ РОГОВИЦЫ ФУКСА

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✧ Эндотелиальная дистрофия роговицы Фукса представляет собой наследственное тяжёлое прогрессирующее заболевание, проявляющееся снижением плотности клеток эндотелия и нарастающим отёком роговицы. Развитие эндотелиальной дистрофии роговицы Фукса может быть связано с увеличением количества тринуклеотидных повторов СТГ в третьем интроне гена *TCF4*. Работа посвящена оценке экспансии СТГ-повторов в гене *TCF4* в российской популяции у пациентов со здоровой роговицей и у пациентов с дистрофией роговицы Фукса (с помощью полимеразной цепной реакции с праймингом тройных повторов и капиллярного электрофореза). Обследован 51 пациент с эндотелиальной дистрофией роговицы Фукса и 38 пациентов без патологии роговицы. Определение количества тринуклеотидных повторов СТГ в гене *TCF4* служит достоверным лабораторным маркером эндотелиальной дистрофии роговицы Фукса.

✧ **Ключевые слова:** эндотелиальная дистрофия роговицы Фукса; *TCF4*; тринуклеотидный повтор; СТГ-повторы; полимеразная цепная реакция с праймингом тройных повторов.

INTRODUCTION

Over the past decades, researchers have made considerable progress in understanding the etiology of endothelial corneal dystrophy (ECD). Fuchs dys-

trophy is the most common form of ECD, occurring in 4%–4.5% of patients older than 50 years [1]. Despite some unresolved issues in the pathogenesis of Fuchs ECD, various genetic aberrations under-

lying its development have been proven. In 2001, L450W and Q455K mutations of the *COL8A2* gene were found to cause an early form of Fuchs ECD. In 2005, researchers confirmed that mutations in the transcription factor 8 (*TCF8*) gene cause posterior polymorphic corneal dystrophy [2, 3]. In addition, various aberrations in the *ZEB1*, *AGBL1*, *LOXHD1*, and *SLC4A11* genes also cause congenital hereditary endothelial dystrophy [4, 5]. However, despite significant progress in gene identification, the exact genetic cause of the mutations responsible for the development of ECD cannot be established in >90% of cases.

In 2010, Baratz et al. proved that the probability of developing Fuchs ECD is significantly higher in carriers of the rs17595731, rs613872, rs9954153, and rs2286812 nucleotide polymorphisms of the *TCF4* gene. These markers helped to differentiate cases of Fuchs ECD with an accuracy of 78%. However, the rs613872 polymorphism is diagnostically the most significant marker for the development of Fuchs ECD [6]. Researchers have found that similar polymorphisms, such as rs17089887, are also associated with Fuchs ECD development in Asian–Chinese [7] and Indian [8] populations, which confirms the hypothesis that the pathogenic genetic anomaly is found in the *TCF4* gene. The *TCF4* gene, located at locus 18q21.2, is involved in regulation mechanisms of intercellular adhesion, cell motility, and cell proliferation [9].

Based on the report by Breschel et al. [10], which described the expansion (increase in number) of CTG trinucleotide repeats in the third intron of the *TCF4* gene of the unstable CTG18.1 region, found in 3% of the population, Wieben et al. [11] in 2012 studied the relationship between expansion at the CTG 18.1 locus and Fuchs ECD. In this study, an increase in the number of CTG repeats of >50 is more strongly correlated with the development of Fuchs ECD than any of the gene loci previously identified. Expansion of the CTG sequence leads to the formation of toxic intranuclear ribonucleic acid (RNA) foci, sequestration of regulatory transcription factors, such as MBNL1,

and splicing disruption (process of excision of certain nucleotide sequences) of RNA [12]. In 2014, after extensive identification of the entire sequence of the *TCF4* gene in patients with Fuchs ECD, other significant genetic mutations within the *TCF4* gene, which would be associated with the development of Fuchs ECD, were impossible to identify (except rs613872 and CTG18.1 trinucleotide repeat) [13]. This confirmed that the expansion of the sequence of CTG trinucleotide directly affects the pathogenesis of Fuchs ECD.

Thus, the expansion of CTG trinucleotide repeats in the third intron of the *TCF4* gene is currently the most promising marker of Fuchs ECD.

This study aimed to assess the prevalence of CTG repeat expansion in the *TCF4* gene in the Russian population in patients with healthy cornea and in patients with Fuchs corneal dystrophy.

MATERIALS AND METHODS

The study included 89 patients aged 50 years who were treated at the Ophthalmology clinic of the Pavlov State Medical University of Saint Petersburg. All participants underwent a standard ophthalmological examination. The patients were categorized into two groups. Group 1 included patients with signs of Fuchs ECD ($n = 51$) (men, 9; women, 42), with a mean age of 69.55 ± 8.54 (range, 50–86) years, with 26, 16, and 9 patients in stages 1, 2, and 3, respectively (Volkov–Dronov classification) [14]. Group 2 (control group) included patients with healthy corneas ($n = 38$) (men, 8; women, 30), with a mean age of 71.11 ± 8.17 (range, 58–88) years (Table 1).

Genomic DNA from all patients was isolated from peripheral blood leukocytes by using a standard protocol to detect the expansion of CTG trinucleotide in the *TCF4* gene [15]. Purified DNA was diluted in an elution TE buffer. When analyzing the DNA concentration, the absorption index of 260/280 in all samples ranged within 1.8–1.9. After the DNA concentration was measured, it was diluted to 100 ng/ μ L and stored at -20°C .

Table 1 / Таблица 1

Patient characteristics Характеристики пациентов

Indicators	Patients with Fuchs dystrophy	Control group
Quantity (men/women)	9/42	8/30
Age (years) \pm SD	69.55 ± 8.54	71.11 ± 8.17
Age variation (years)	50–86	58–88

The number of CTG repeats in the *TCF4* gene was determined in two stages: screening using the classical polymerase chain reaction (PCR) method and confirmation of PCR expansion with triple repeat priming.

Flanking primers, which bind to sites beyond the expansion zone, were synthesized to perform a screening study of the number of CTG repeats in the *TCF4* gene. One of the primers was labeled with FAM 6. The upstream primer bordered the 5'-end of the CTG repeat region. The downstream primer was a gapper capable of hybridizing with any region of the CTG repeat site.

The nucleotide sequences of primers, concentration of PCR mixture components, and conditions for screening PCR and PCR with triple repeat priming are detailed in previous studies [16, 17].

Fragment analysis was performed using an ABI PRISM 3500 genetic analyzer (Applied Biosystems) to separate the reaction products after screening PCR and PCR with triple repeat priming.

Initially, a screening study was performed for the precise determination of the number of CTG repeats. To calculate the number of CTG repeats, 230 nucleotides, which comprise the size of the primers, and nucleotides before the onset of the expansion locus, were subtracted from the size of the PCR product obtained. The number of CTG repeats was calculated using the following formula:

$$CTG_n = \frac{\text{fragment size} - 230}{3}$$

The presence of the expansion of CTG repeats in the *TCF4* gene was excluded to determine two alleles (Fig. 1).

The patient was considered to be a carrier of heterozygous expansion if the number of CTG repeats on one of the alleles exceeded 50. Differentiation between the same number of repeats on both alleles and expansion was required to detect one allele (Fig. 2). Thus, expansion was confirmed by PCR with triple

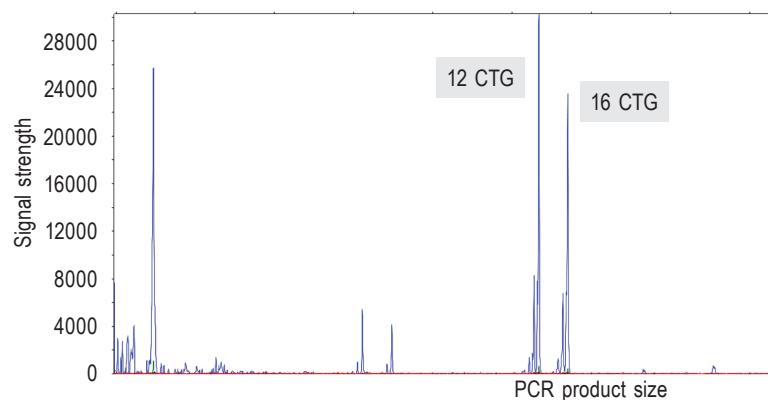


Fig. 1. Electrophoregram of the screening study of the number of CTG repeats in the *TCF4* gene. Patients have no expansion of CTG repeats in the *TCF4* gene

Рис. 1. Электрофореграмма скринингового исследования количества CTG-повторов в гене *TCF4*. Пациенты не имеют экспансии CTG-повторов в гене *TCF4*

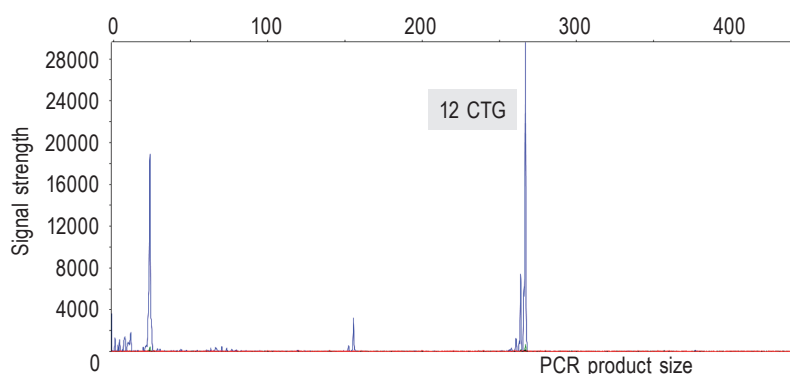


Fig. 2. Electrophoregram screening study of the number of CTG repeats in the *TCF4* gene. Expansion required

Рис. 2. Электрофореграмма скринингового исследования количества CTG-повторов в гене *TCF4*. Требуется исключение экспансии

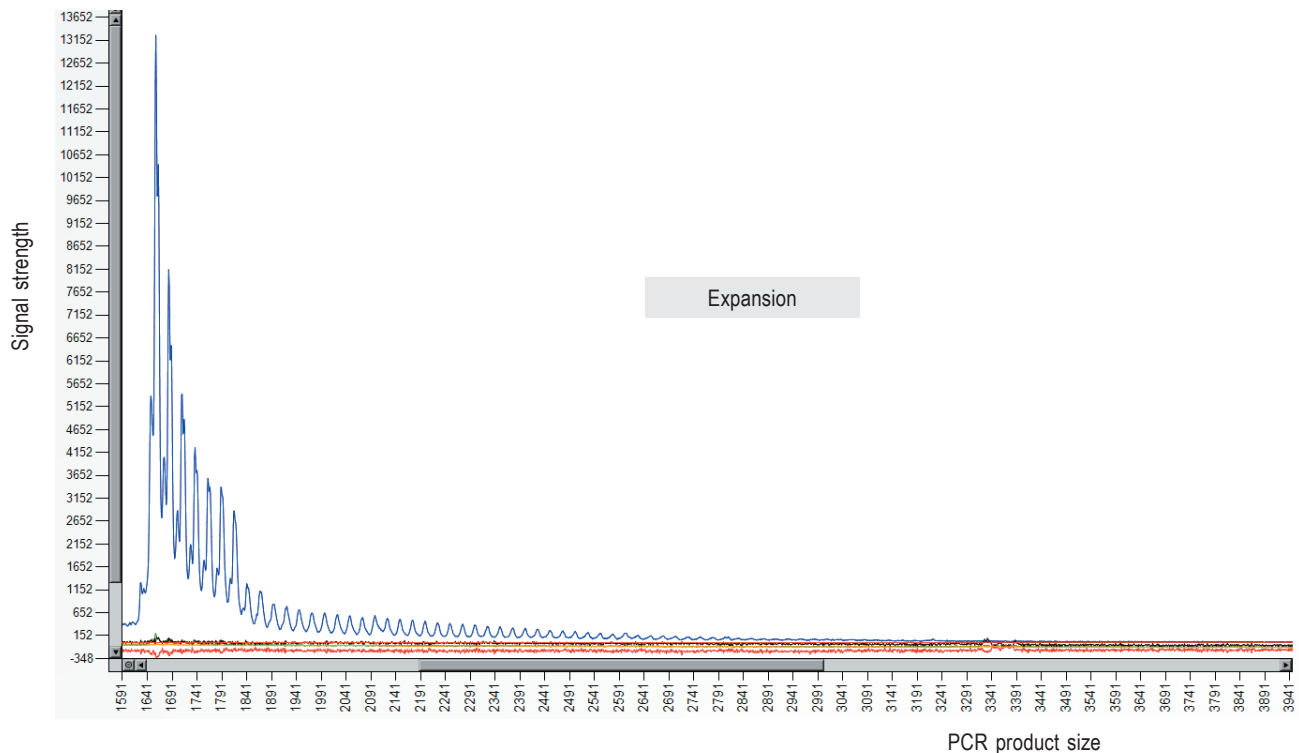


Рис. 3. PCR electrophoregram with triple repeat priming in a patient with an expansion of CTG repeats in the *TCF4* gene

Fig. 3. Электрофореграмма ПЦР с праймингом тройных повторов у пациента с экспансией CTG-повторов в гене *TCF4*

repeat priming. No expansion was detected during PCR with triple repeat priming if the patient had the same number of repeats on two alleles.

During the expansion of CTG repeats in the *TCF4* gene on one of the alleles, a typical picture of the electrophoregram, shown in Fig. 3, was noted.

In the absence of peaks in the electrophoregram after screening and the presence of a positive pattern, homozygous expansion was determined in patients by confirming PCR reaction.

Statistical analysis was performed using the Graph Pad 6.0 program. The χ^2 test was used to compare the qualitative characteristics of the groups. The results were presented as the median and interquartile range. The results were considered statistically significant at $p < 0.05$.

RESULTS

The expansion in the group of patients with Fuchs ECD was 55%. In addition, a homozygous

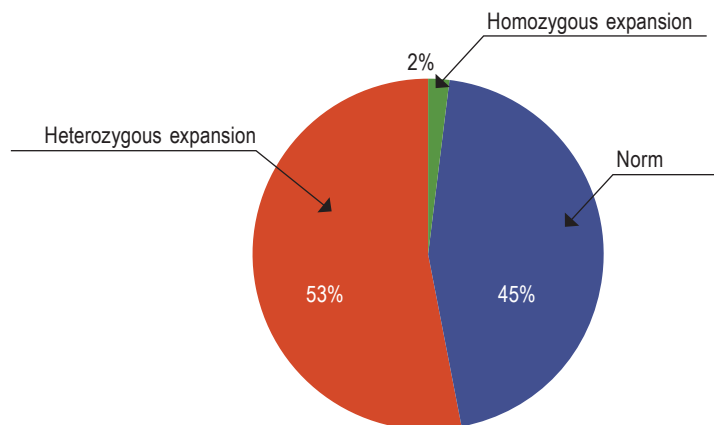


Fig. 4. The prevalence of expansion of CTG repeats in the *TCF4* gene in the group of patients with FECD

Fig. 4. Распространённость экспансии CTG-повторов в гене *TCF4* в группе пациентов с эндотелиальной дистрофией роговицы Фукса

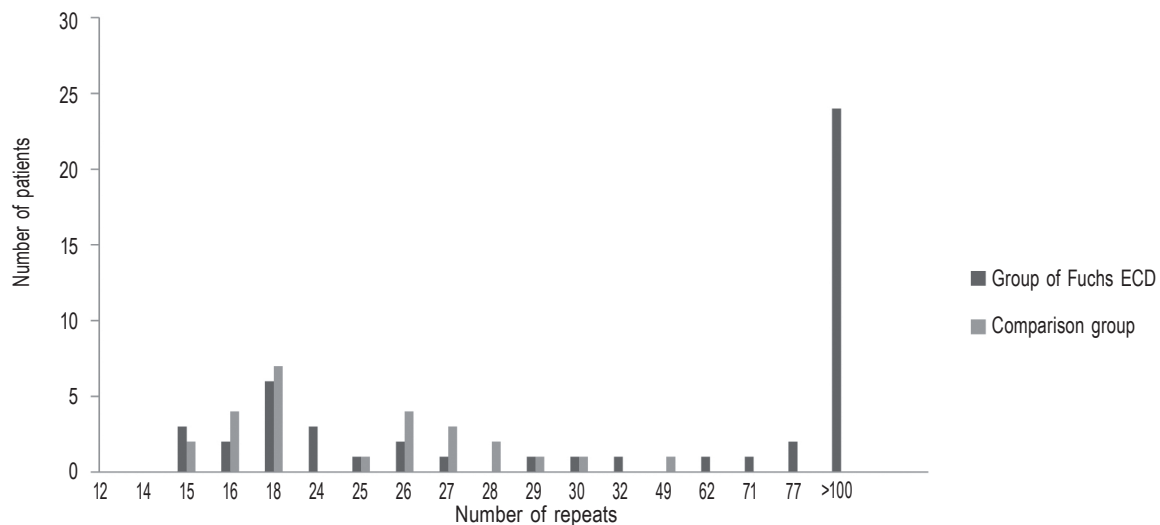


Fig. 5. The number of repetitions in the group of patients FECD and the comparison group

Fig. 5. Количество CTG-повторов в группе пациентов с эндотелиальной дистрофией роговицы Фукса и в группе сравнения

pathological increase in the number of repeats was detected in one patient. In the control group, an increase in the number of CTG repeats of >50 was not registered. The data obtained are presented in Fig. 4 and Fig. 5. The characteristics of patients from the control and Fuchs ECD groups are presented in Table 1.

DISCUSSION

Fuchs ECD ranks high as an indication for corneal transplantation in the United States [18]. Currently, one of the main reasons for the development of Fuchs ECD may be an increase in the number of CTG repeats in the third intron of the *TCF4* gene [19]. However, the penetrance and expressiveness of the mutation can vary significantly in different patients. Carriership of heterozygous or homozygous expansion without objective signs of Fuchs ECD increases the risk of the disease development by 76 times [20].

The pathogenesis of *TCF4*-associated Fuchs ECD is based on the formation of toxic mRNA with expansion CTG repeats of intranuclear formations that disrupt normal RNA homeostasis of the cell by adsorption of splicing factors, mainly MBNL1 [12]. In several experiments on the corneal endothelial cell lines of patients with Fuchs ECD, MBNL1 and MBNL2 proteins have been shown to be co-localized with the *TCF4* gene mRNA foci. In patients with *TCF4* gene mutation, the corneal endothelial cells were characterized by an altered mRNA splicing pattern compared with patients with Fuchs ECD without expansion. This finding confirmed that splicing is impaired due to CTG expansion rather than disease progression [12].

In addition, the toxicity of expansion mRNA of the *TCF4* gene was proven by transfection of the *TCF4* gene with an increased number of CTG repeats in human corneal endothelial cell lines. This modification not only caused the formation of mRNA foci, but also led to changes in the cells characteristic of Fuchs ECD. The importance of the participation of CTG expansion in the Fuchs ECD pathogenesis is also emphasized by the ability to block the development of Fuchs ECD in cell models by the addition of inhibitory antisense (CAG) 7 of mRNA [21].

The present research, which focused on the study of the prevalence of expansion in the *TCF4* gene in patients with Fuchs ECD and patients without signs of corneal dystrophy, is one of the first studies conducted in the Russian Federation. The incidence of heterozygous expansion in the study group of Fuchs ECD was 53%, which was comparable with a number of studies conducted in the United States and Europe. Thus, the prevalence of expansion of CTG trinucleotides in patients with Fuchs ECD in different ethnic groups [8, 17, 22–25] ranges from 34% to 73%. In the Russian population, the only data on the frequency of occurrence of CTG trinucleotide expansion in patients with Fuchs ECD [26] coincide with global data (66.7%). However, the prevalence of this aberration in the Russian population without signs of Fuchs ECD has not been shown in any study. The prevalence of homozygous expansion in this study was 2%, which was also comparable with the results of previous studies [25, 26]. In addition, we showed that the control group, which included patients without corneal pathology, had no mutations, which was

consistent with previous studies [7, 8, 24]. However, expansion in the *TCF4* gene was present in 2%–7% of cases in studies involving larger sample sizes of patients in the comparison group. The presence of aberrations in the control group can be explained by the low level of penetrance and expressivity of the mutation under study.

CONCLUSION

Fuchs ECD, which had an unclear pathogenesis until recently, is a common ophthalmic disease in patients older than 40 years, and the diagnosis was based solely on clinical and instrumental data. However, in most patients, the description of a new pathogenic aberration in the form of expansion in the *TCF4* gene not only confirmed the diagnosis but also created new etiological approaches for treatment.

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There is no conflict of interest.

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