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RELATIONSHIP OF THE TYPE AND POSITION OF MUTATION IN THE *FBN1* GENE WITH CLINICAL MANIFESTATIONS OF MARFAN SYNDROME IN CHILDREN

Marfan syndrome (OMIM # 154700) is an inherited connective tissue disease caused by mutations in the FBN1 gene, characterized by marked clinical variability, the causes of which are poorly understood.

The aim of this study was to determine the association of the type and localization of the *FBN1* gene mutation with the severity of clinical manifestations of Marfan syndrome in a Russian cohort of children.

Results: for the first time in a Russian cohort of children, the association between the type and localization of the *FBN1* gene mutation and the severity of clinical manifestations was demonstrated: LoF mutations lead to greater damage to the cardiovascular and skeletal systems; missense mutations lead to greater damage to the eyes. Mutations in exons 1-10 lead to the earliest onset of skeletal changes (foot (p=0.016) and chest (p=0.036) deformities), mutations in exons 11-20 - to the earliest appearance of lens ectopia (p=0.034), with less severe dolichostenomelia (p=0.041) and less frequent formation of aortic dilatation (p=0.035). Mutations in exons 21-35 are accompanied by the earliest manifestation of spinal deformity (p=0.02). Mutations in exons 51-66 less often lead to lens ectopia (p=0.001).

Keywords: *FBN1* gene, missense mutations, LoF (loss of function) mutations, TGFβ (transforming growth factor β), children, Marfan syndrome

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Introduction. Marfan syndrome (OMIM # 154700) is an autosomal dominant connective tissue disease with a prevalence of 1:5000 [2] in the population, based on mutations in the *FBN1* gene encoding fibrillin-1, a component of the extracellular matrix. A distinctive feature of Marfan syndrome is the marked variability of clinical manifestations.

Since the discovery of the *FBN1* gene in 1991 [5], studies have been conducted on laboratory animals with Marfan syndrome to study the influence of the type of *FBN1* gene mutation on clinical manifestations. In mouse models with LoF (loss of function) mutations, pronounced aortic and skeletal damage was proved [8]. Myxomatous thickening of atrioventricular heart valves was detected in mice with missense mutations [7]. The explanation for the variability of symptoms in mice with different types of *FBN1* gene mutations was differently changed activity of TGFβ (transforming growth factor β) signaling pathway, which is one of the main pathogenetic mechanisms of complications in Marfan syndrome [4-6]. In laboratory animals, mice with LoF mutations have been shown to have more altered TGFβ signaling pathway activity than missense mutations, resulting in variable clinical manifestations.

In the last decade of the XXI century, studies of the effects of the type and localization of the *FBN1* gene mutation were conducted on large groups of patients with Marfan syndrome of different ages. It has been confirmed that LoF mutations have a greater impact on the aorta than missense mutations [1-3], including a larger average diameter of the aortic root, a higher risk of aortic dissection or the need for surgical intervention. Also, patients with LoF mutations, in contrast to patients with missense mutations, were found to have taller stature, more severe arachnodactyly and dolichostenomelia, and a higher incidence of thoracic and high palate deformities [1-3]. At the same time, patients with Marfan syndrome with missense mutations had a higher incidence of lens ectopia [3]. Moreover, it was proved that patients with Marfan syndrome with missense mutations with cysteine loss, in contrast to patients with missense mutations without cysteine involvement, had larger aortic dimensions and a higher incidence of arachnodactyly [3].

In addition to the type of *FBN1* gene mutation, the relationship between the localization of *FBN1* mutation and clinical symptoms in Marfan syndrome has been studied. By now it has been proved that localization of *FBN1* gene mutation in exons 24-32 leads to especially severe clinical manifestations. The presence of a missense mutation with cysteine loss in

these exons aggravates the course of the disease with a higher frequency of surgical interventions on the aortic and mitral heart valves, a higher frequency of surgical correction of the visual organ, and more pronounced skeletal deformities [1-3]. The influence of other localizations of *FBN1* gene mutations has not been proven yet.

Thus, the study of the influence of the type and position of the *FBN1* gene mutation on the severity and spectrum of clinical manifestations in Marfan syndrome contributes to a better understanding of the pathogenesis of the disease and, consequently, to the search for new targets for therapy. This study makes it possible to determine the criteria of prognosis of the course of the disease, which is especially important in children. Reasoned planning of targeted dispensary monitoring of sick children will ensure early diagnosis of emerging complications and their timely treatment.

The aim of this study was to determine the association of the type and localization of the *FBN1* gene mutation with the severity of clinical manifestations of Marfan syndrome in a Russian cohort of children.

Patients and methods. Patient cohort. From October 2021 to December 2023, 72 children, aged 0 to 18 years, with clinical signs of Marfan syndrome were consecutively hospitalized at the Clinical Genetics Department of the Veltischev Institute. All children were evaluated using the revised Ghent criteria [10]. Marfan syndrome was confirmed in 72 children. The mean age in the group was 12 years; 35 girls and 37 boys were included in the study.

Clinical research methods. All patients had a thorough history of the disease, in particular, the age of onset of organ system lesions characteristic of Marfan syndrome. All children underwent a physical examination with calculation of the connective tissue systemic lesion score [10]. According to the Ghent criteria, a score of ≥7 is diagnostically significant and belongs to the large Ghent criteria.

Functional studies of the cardiovascular system. All children underwent transthoracic echocardiography with evaluation of cardiac and vascular anatomy with calculation of the Z criterion for aortic root dimensions.

Molecular genetic study. Molecular genetic study was performed on all 72 (100%) children. Full genome sequencing in Evogen laboratory, thanks to the financial support of the Genome of Life charitable foundation, was performed n=25 (32%) in the group. Full-exome sequencing was performed n=10 (14%) in the group. Study of a panel of 166 genes responsible for bone pathology - n=29 (43%) in the laboratory of the Medical and Genetic Research Center named after Academician N.P. Bochkov. Target sequencing of FBN1 gene - n=8 (11%) in the group.

Statistical analysis. Statistical analysis of the data was performed using IBM SPSS Statistics 26.0 program.

Results. Molecular genetic study revealed LoF mutations in 42 (58%) children, which included large deletions, including complete absence of *FBN1* gene, splice site mutations, frameshift mutations, nonsense mutations. Missense mutations were identified in 30 (42%) children, among which: 14 with cysteine loss and 16 without cysteine involvement.

Depending on the localization of the *FBN1* gene mutation, children were divided into 5 groups: 1) group of children with mutations in exons 1 through 10, total - 11 (15%) children, including: with LoF mutations - 4(36%), with missense mutations - 7(64%); 2) group of children with mutations in exons 11 through 20, total in the group - 14 (19%) children, of which with LoF mutations - 8 (57%), with missense mutations - 6 (43%); 3) a group of children with mutations in exons 21 through 35, total in the group - 10 (14%) children, among which with LoF mutations - 5 (50%), with missense mutations - 5 (50%); 4) group of children with mutations in exons 36 through 50, total in the group - 18 (25%) children, among them with LoF mutations - 12(67%), with missense mutations - 6(33%); 5) group of children with mutations in exons 51

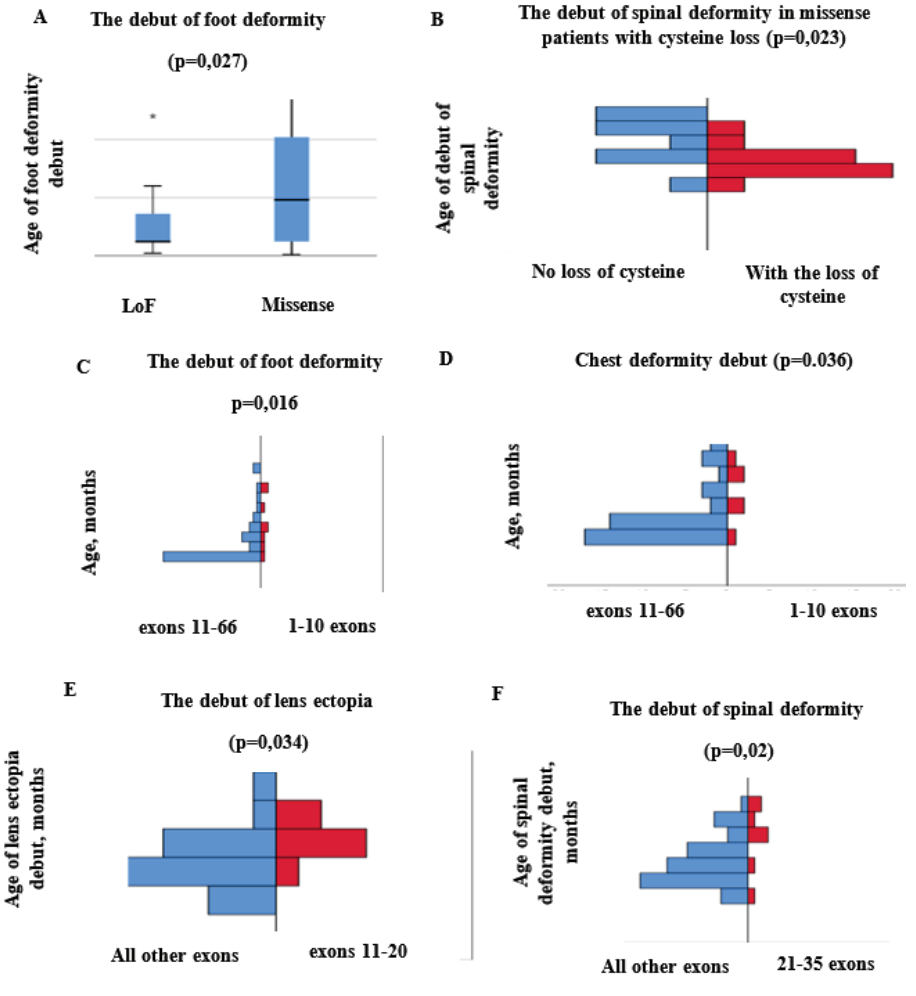

Fig. 1. Statistically significant differences between the compared groups regarding the debuts of clinical features: 1A - comparison of children with missense and LoF mutations by age of foot deformity debut; 1B - comparison of children with missense mutations with and without cysteine loss by age of spinal deformity debut; 1C and 1D - comparison of children with mutations in exons 1-10 with the rest of the children by time of spinal (1C) and thoracic (1D) deformity debuts; 1E - comparison of children with mutations in exons 11-20 with the rest of the children by time of debut of lens ectopia; 1F- comparison of children with mutations in exons 21-35 with the rest of the children by age of debut of spinal deformity.

through 66, total in the group - 19 (26%) children, among them with LoF mutations - 13(68%), with missense mutations - 6(32%) children.

To determine the influence of mutation type and localization on the spectrum of clinical manifestations in children with Marfan syndrome, we compared groups of 1) children with LoF and missense mutations, 2) children with missense mutations with and without cysteine loss, and 3) groups of children formed according to the localization of the mutation in the *FBN1* gene.

Study of the age of debut of clinical manifestations in different FBN1 gene mutations. Regarding the debut of clinical signs, it was revealed that children with LoF mutations, in contrast to children with missense mutations, have significantly earlier onset of foot deformities (up to 3 years of age) (p=0.027) (Figure 1A); children with missense mutations with cysteine loss, in contrast to children with missense mutations without cysteine involvement, have earlier onset of spinal deformities (up to 6 years of age) (p=0.023) (Figure 1B). Children with mutations in exons 1-10 show earlier deformities of both feet (up to 3 years of age) (p=0.016) (Figure 1C) and chest (up to 5 years of age) (p=0.036) (Figure 1D); children with mutations in exons 11-20 manifest lens ectopia earlier than others (up to 5 years of age) (p=0,034) (Figure 1E); with mutations in exons 21-35, spinal deformity is detected earlier than others (up to 6 years of age) (p=0,02) (Figure 1F).

Study of the severity of clinical manifestations in different FBN1 gene mutations. When examining the severity of cardiovascular damage, it was found that children with LoF mutations had larger aortic root sizes compared to children with missense mutations (p=0.003) (Figure 2A), and were significantly more likely to have aortic dilatation (Z-criterion for aortic size ≥3) (p=0.02). Children with missense mutations with cysteine loss had larger aortic root size compared to children with missense mutations without cysteine involvement (p=0.046) (Figure 2B). Children with mutations in exons 11-20 were less likely than others to have aortic dilatation (p=0.035). A negative effect of missense mutations was revealed in the form of greater mitral valve damage (p=0.04).

Regarding the severity of skeletal lesions, it was shown that children with LoF mutations more often than those with missense mutations had foot deformities (p=0.01), keeled chest deformity (p=0.004), and more pronounced dolichostenomelia (p=0.023) (Figure 2C). Children with mutations in exons 11-20 showed less pronounced dolichostenomelia (p=0.041) (Figure 2D).

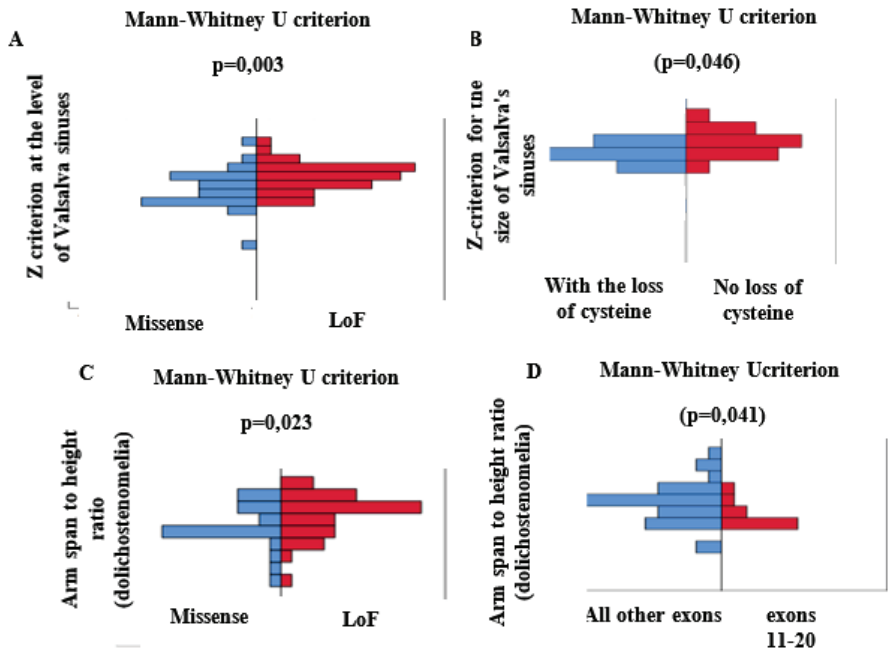

Fig. 2. Statistically significant differences between the compared groups with respect to clinical features: 2A, comparison of children with missense and LoF mutations with respect to aortic size at the level of Valsalva sinuses; 2B, comparison of children with missense mutations with and without loss of cysteine with respect to aortic size at the level of Valsalva sinuses; 2C, comparison of children with missense and LoF mutations with respect to dolichostenomelia; 2D, comparison of children with mutations in exons 11-20 with the rest of the children with respect to dolichostenomelia.

With regard to vision, it was found that: children with missense mutations were significantly more likely than those with LoF mutations to have lens ectopia (p=0.006); children with LoF mutations were more likely than those with missense mutations to have severe myopia (p=0.001). Children with mutations in exons 51-66 had lens ectopia less often than the others (p=0.001).

Discussion of the results. The study yields both new correlations and confirmation of previously found correlations.

In the present study, children with LoF mutations have been shown to have larger aortic dimensions and greater skeletal damage than children with missense mutations. From the pathogenetic point of view, the relationship between this spectrum of clinical manifestations and LoF mutations can be explained by extrapolating the results of studies of mice with Marfan syndrome, which showed that the activity of TGFβ signaling pathway is more altered in LoF mutations than in missense mutations [4,7]. In contrast, lens ectopia is more common in missense mutations, according to the results of this study. It is known that the cinnova ligament, which anchors the lens, consists only of fibrillin microfibrils. In missense mutations, defective fibrillin-1 is synthesized, which leads to the formation of a failed cinnova ligament, resulting in lens ectopia. Consequently, impaired structural function of fibrillin-1 underlies this manifestation.

In addition to a better understanding of the pathogenesis of Marfan syndrome, the correlations identified may help to shape the prognosis of the disease. Thus, according to the results of our study, children with LoF mutations have an earlier debut and frequency of foot deformities and larger aortic dimensions. Given that skeletal signs manifest earlier than cardiovascular manifestations [9], children with early manifestation of foot deformity (before 3 years of age) and suspected Marfan syndrome should be recommended to be seen by a pediatric cardiologist as early as possible without waiting for the results of molecular genetic testing. Similarly, children with early onset of spinal deformity (before 6 years of age) and suspected Marfan syndrome should be recommended for pediatric cardiology follow-up, as early spinal cord involvement is characteristic of children with missense mutations with cysteine loss, who also have greater aortic involvement than children with missense mutations without cysteine involvement.

The correlations between the debut and the spectrum of clinical signs with

the localization of the *FBN1* gene mutation identified in this study can also help in planning the dispensary follow-up of children with Marfan syndrome. For example, children with mutations in exons 1-10 should be monitored by an orthopedic traumatologist for foot and thoracic deformities, and children with mutations in exons 21-35 should be monitored for spinal deformities. Earlier observation by an ophthalmologist is recommended for children with mutations in exons 11-20 due to the risk of lens ectopia.

Conclusion. The study of the influence of the type and localization of the *FBN1* gene mutation on the severity and spectrum of clinical manifestations in Marfan syndrome may contribute to a better understanding of the pathogenesis of this disease, the formation of prognosis of its course and planning of dispensary follow-up. In the present study, for the first time in a Russian cohort of children with Marfan syndrome, the influence of the type and localization of the *FBN1* gene mutation on the clinical manifestations of the cardiovascular, ocular, and skeletal systems was proved. Further study of the influence of the patients' genotype on other organ systems in this disease is planned.

Conflict of interest. The authors declare that there are no obvious and potential conflicts of interest related to the publication of this article. Parents of all children participating in the study signed informed consent.

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INFLUENCE OF UTERINE FIBROID ON UTERINE BLOOD FLOW, MENSTRUAL FUNCTION AND FEATURES OF REPRODUCTIVE HEALTH DISORDERS IN WOMEN

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The study was conducted on women aged 18-45 years old with uterine fibroids and impaired reproductive function. In patients with uterine fibroids, menarche began at an earlier age and cyclic bleeding was more often observed, causing posthemorrhagic anemia. Reproductive function disorders were caused by infertility and miscarriages. Indicators of S/D, RI, PI of the uterine artery in the presence of fibroids were lower than in the group of healthy women. In group I, primary infertility predominated, and in group II, secondary infertility prevailed. Thus, risk factors for reproductive potential in women with uterine fibroids have been studied, early diagnosis has been established, and it has been determined that it is important to choose adequate treatment tactics to achieve the realization of reproductive desires.

Keywords: uterine fibroids, benign diseases of the uterus, reproductive potential disorders, dopplerography of the uterine arteries.

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Introduction. Uterine fibroids are among the most common benign tumors affecting the female reproductive system. The detection rate of uterine fibroids in women reaches 60% by age 35 and more than 80% by age 50 [13]. The presence of myomatous nodes adversely affects the reproductive function of women and negatively affects the somatic health of patients and their quality of life [1]. In addition, risk factors for the development of uterine fibroids include race and ethnicity, family history, early menarche and late menopause, obesity, stress, hypertension, exposure to environmental toxins, and vitamin D deficiency [7,9]. Most women with uterine fibroids do not have any special complaints, but a third of patients experience serious symptoms such as uterine bleeding with secondary anemia, pelvic pain, infertility and recurrent miscarriages [8]. Ultrasonography, preferably transvaginal, is the first-line method for diagnosing uterine fibroids [5]. Approximately 60% of patients with uterine fibroids experience clinical mani-

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