HYPERTROPHIC CARDIOMYOPATHY: GENETIC CHANGES, PATHOGENESIS AND PATHOPHYSIOLOGY

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Abstract. *This review is devoted to the description of genetic changes, pathogenetic mechanisms and pathophysiology of hypertrophic cardiomyopathy based on the analysis of the latest published data. The current data on the role of identified numerous mutations of structural, structural and regulatory sarcomere proteins in the pathogenesis of cardiomyopathy are presented. The main hypotheses of the pathogenetic process are highlighted, special attention is paid to the violation of the regulation of calcium metabolism. The importance of genetic testing in patients with hypertrophic cardiomyopathy and their relatives is emphasized.*

Keywords: *troponin T, troponin I.*

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disease characterized by severe hypertrophy of the predominantly left ventricle (LV) with the absence of dilation of the heart chambers without signs of other cardiac pathology or systemic diseases responsible for the development of hypertrophy [1–4]. On average, the prevalence of HCMP is estimated as 1:500 people [1, 4]. Despite the simple definition and relatively simple diagnosis of this form of cardiomyopathy, interest in its study continues to grow, due to a number of reasons. In particular, to date, more than 1400 different gene mutations have been identified in patients with HCMP, mainly sarcomere proteins, which suggests the presence of genetic heterogeneity of this disease [4-6]. Since the first description of the mutation of the myosin heavy chain gene, there has been a kind of “research breakthrough defining the genetic substrate of the disease, accompanied by significant optimism and expectations that mutation analysis will be able to revolutionize the idea of HCMP in terms of diagnosis, prediction of the clinical course, as well as the direction of treatment of this pathology” [5]. However, numerous gene mutations discovered do not allow us to answer a number of important questions. In particular, no reliable correlations were found between genetic defects and variants of phenotypic manifestations of the disease.

It is still unclear why, despite the hereditary type of cardiomyopathy, not all cases of identified genetic defects and not all direct relatives of patients have the development of GCMP. Even a new category of patients has been designated: “genotype-positive and phenotype-negative” [7, 8]. Moreover, the question of time and factors determining the clinical manifestations of the disease in cases of detection of genetically mutated sarcomere proteins at birth and during life remains unclear. An accurate and complete understanding of the pathophysiological features of HCMP is necessary to understand the clinical picture of the disease, its timely diagnosis, monitoring of the development process and, above all, the development of adequate therapeutic approaches. This review is devoted to the description of genetic changes, pathogenetic mechanisms and pathophysiology of HCMP based on the analysis of the latest published data. Genetic changes in 1990, a mutation -myosin heavy chain gene (MYH7) was first described, which for some time of the was considered the only cause of the development of this form of cardiomyopathy [9]. After a little less than a quarter of a century of intensive searches, a very

“extensive and stunning heterogeneity of the genetic substrate of HCMP” was discovered [5]. To date, at least 13 patients with HCMP have been identified genes with more than 1400 mutations expressed mainly or exclusively in the heart tissues causing this disease [5, 8]. Genetic testing of the 10 most frequently encountered genes makes it possible to make a genetic diagnosis in about 60% of patients, family members of patients with HCMP, and the detected gene mutations are responsible for coding in the main proteins of thick and thin myofilaments. In patients with a positive genetic test, mutations of proven or doubtful pathogenicity were found in about 70-80% of cases in the two most common genes — the heavy chain -myosin (MYH7) and myosin-binding® protein C (MYBCP3), while mutations of other -αgenes, including troponin T, troponin I, -cardiac actin, are responsible for the pathologyαtropomyosin and of only a small part of patients (1-5%) [5, 6, 12, 13]. Interestingly, to date, no reliable correlations have been found between gene mutations and the corresponding phenotypic phenomena of the disease, which is probably due to the genetic and clinical heterogeneity observed in HCMP [12, 14, 15]. Nevertheless, it is believed that a more severe course of cardiomyopathy, estimated by the frequency of cardiovascular mortality, cerebral circulation disorders, disease progression and severity of LV systemic dysfunction, is more often observed in patients with HCMP with sarcomere mutations than among patients without identified genetic defects [14, 16]. Moreover, patients with more than one mutation (approximately 5% of all cases) have a more severe course of the disease, especially in the presence of triple mutations and homozygosity [17]. Mutations of genes encoding molecules that interact with sarcomere proteins have been studied in detail in recent years for their relationship with HCMP [14]. At the same time, much attention is focused on the proteins represented in the Z-disk connecting the sarcomeres with each other. To date, changes in the genes encoding, in particular, titin (TTN), muscle protein LIM (CSRP), teletonin (TCAP) and myosein 2 (MYOZ2), causing the development of the disease, have already been identified [6, 13, 18]. In some cases, functional studies of newly discovered variants of the sequence of amino acid residues mean that they disrupt the interaction in the chain “protein-protein". For example, damaged titin residues found in HCMP demonstrate high binding affinity to actinin or cardiac ankyrin R, which plays an important role in the processes of recovery and regeneration of muscle tissue in response to stress and damage [14]. There is uncertainty in determining the relationship of specific mutations, mainly the MYH7 gene, with variants of clinical manifestations of the disease. Whatever terms of these mutations are used - “malignant”, “benign", “more severe” phenotype at the onset of cardiomyopathy at a young age, severe LV hypertrophy or a high risk of sudden cardiac death (SCD) - their widespread introduction into clinical practice is considered premature. These definitions were obtained mainly according to the data of the conducted studies performed with significant limitations: a small population of patients, a low frequency of registration of a particular mutation in relation to the clinical group.

Despite the huge number of identified mutations in patients with HCMP and their family members, the question remains how these changes can cause the development of the disease. In particular, it remains a mystery how a single nucleotide substitution in a sarcomere protein leads to the development of HCMP. It is also unclear why clinical manifestations of the disease occur many years later, despite the expression of the mutated protein already at birth or at the beginning of human life. It is noted that in “genotype-positive” individuals, LV hypertrophy may develop by the sixth or seventh decade of life, and some carriers of HCMP mutations do not occur at all [4, 7, 21].

Pathogenetic mechanisms. Several pathogenetic hypotheses have been proposed to explain the relationship between sarcomere gene mutations and the development of HCMP. Thus, experimental models and recently obtained analyses of cardiac tissue sections of healthy volunteers and individuals suffering from this cardiomyopathy indicate a decrease in the level of myosin-binding protein C in cardiac tissue with a missense mutation of MYBPC3 amino acid residues or a shortened mutation [22]. These data allow us to assume that haplon-sufficiency of MYBPC3 or a decrease in the amount of a functionally complete protein due to a dominant mutant gene inactivating one allele is one of the pathological mechanisms of HCMP. On the other hand, studies of most other sarcomere mutations mean that at normal protein levels, their function is changed. Bio- physical properties of mutated sarcomeres MYH7, are characterized by a significant enhancement of their function. At the same time, myosin proteins containing mutations typical of HCMP cause an increase in ATP-az activity, the generated contraction force and increased sliding of actin filaments [14]. Cardiac Troponin 2 mutation (TNNT2) has a similar effect: it is accompanied by the activation of ATP-aza and an increase in strength abbreviations of sarcomeres [23]. The consequences of the altered biophysical properties of contractile proteins can directly affect the performance of sarcomeres, the cellular biology of myocytes and energy processes in the myocardium. Due to the simultaneous presence of both mutated and normal proteins in sarcomas, regulated contractility can become disorganized. Biophysical changes in mutated sarcomeres cause disturbances of intracellular calcium metabolism (Ca 2+), predisposing to the occurrence of arrhythmias, which is confirmed by experimental and clinical data [24, 25]. Increased ATPASE activity due to sarcomere mutations may also cause a higher myocardial energy demand, with inadequate replenishment of which accelerated myocyte death occurs with the formation of focal scar changes in the myocardium [26]. A violation of the regulation of intracellular Ca 2+, as the main modulator of myocyte contraction and relaxation, can activate hypertrophy and dysfunction of the myocardium exposed to stress [27]. Experimental models of GCMP reveal a change in the content of intracellular Ca 2+, including a decrease in its level in the sarcoplasmic reticulum and an increase in the concentration of cations in the diastole [23, 28]. Violations of the regulation of Ca 2+ under experimental conditions, hypertrophic remodeling of the myocardium precedes, and the results of long-term studies indicate that early pharmacological corrections that normalize the dysregulation of Ca 2+ metabolism slow down the development and severity of myocardial hypertrophy [14]. Recently F. Lan et al. (2013) suggested that disruption of Ca 2+ metabolism in general and an increase in its concentration inside the cell are central mechanisms in the pathogenesis of HCMP [24]. In connection with these biochemical and clinical data, the question arises which pathogenetic mechanisms are activated due to a violation of the regulation of Ca 2+ in myocytes in this disease. In recent years, a lot of scientific evidence has been accumulated confirming that mutations of sarcomere proteins, in particular thin filaments (for example, mutations of cardiac troponin T), actually increase the sensitivity of contractile elements to Ca 2+ and enhance the force of contraction [29, 30]. Biophysical analysis of mutated sarcomere proteins, which are “hypercontractile”, with overestimated energy costs for the production of contraction force, led researchers to a more specific hypothesis: the molecular basis of HCMP is represented by cellular energy deficiency, as a result of the uneconomical function of sarcomeres [30, 31]. Altered biophysical forces and an imbalance of intracellular Ca 2+ in myocytes, along with increased energy requirements, expose myocytes to increased stress in GKMP. Among the hypotheses explaining the relationship between mutations of sarcomere

proteins and the development of morphological changes in HCMP, the following is considered the most convincing.

Mutations cause violations of myocyte contractility, which leads to diastolic and systolic myocardial dysfunction, causing increased stress of the walls of the ventricles, a decrease in shock volume and, in turn, activates stress-induced trophic and mitotic factors (angiotensin-converting enzyme 1, angiotensin 2, insulin, growth factor 1, transforming growth factor, interleukin-6 and endothelin). Theseαtumor necrosis factor- factors contribute to an increase in the input of Ca 2+ into the cell and activation of transcription pathways, which lead to various histological and structural phenotypes of HCMP, including myocardial hypertrophy, multidirectional arrangement of myocytes and interstitial fibrosis [32].

REFERENCES

1. Лапасов С. Х. и др. Инновационные подходы в диагностике язвенной болезни у взрослых в первичном звене здравоохранения: обзор литературы //Здоровье, демография, экология финно-угорских народов. – 2018. – №. 4. – С. 68-72.
2. Utkurovna S. G. et al. The condition of pro-and antioxidant systems in children with acute laryngotracheitis with immunomodulating therapy //Достижениянаукииобразования. – 2019. – №. 10 (51). – С. 37-40.
3. Kurbonova G. A., Lapasova Z. K. CURRENT VIEWS ON IRON DEFICIENCY ANAEMIA IN PATIENTS WITH
4. CARDIOVASCULAR DISEASE //The American Journal of Medical Sciences and Pharmaceutical Research. – 2022. – Т. 4. – №. 03. – С. 59-64.
5. Khidirovna L. Z. et al. Significance of Syndrome Teetering in Development of Residual Pain Syndrome in Patients Operated for Lumbar Osteochondrosis //Texas Journal of Multidisciplinary Studies. – 2022. – Т. 6. – С. 59-63.
6. Sherali K., Zebiniso L., Gulbahor K. Features Of Anthropometric Indicators Of Children Of The First Year Of Life Born Of Mothers In The State Of Hypothyrozis //The American Journal of Medical Sciences and Pharmaceutical Research. – 2020. – Т. 2. – №. 09. – С. 64-68.
7. ЛапасоваЗ. Х. идр. Юрак қон томир касалликлари ривожланишига олиб келувчи хавф омилларини ўрганиш. Биология ва тиббиёт муаммолари //Халкаро илмий журнал. – 2019. – С. 213-215.
8. Лапасов С. и др. Кишлок врачлик пункт ишароитида 45-65 ёшли юрак ишемик касалигига мойиллиги бор ахолини эрта аниклаш жараёни сифат курсаткичини яхшилаш //Журнал проблемы биологии и медицины. – 2013. – №. 1 (72). – С. 50-53.
9. Юлдашова Н. и др. Диагностика и лечение осложнений сахарного диабета на основе принципов доказательной медицины //Журнал проблемы биологии и медицины. – 2018. – №. 3 (102). – С. 192-197.
10. Khidirovna L. Z. et al. Significance of Syndrome Teetering in Development of Residual Pain Syndrome in Patients Operated for Lumbar Osteochondrosis //Texas Journal of Multidisciplinary Studies. – 2022. – Т. 6. – С. 59-63.
11. Nematjon M. УМУМИЙ АМАЛЁТ ШИФОКОРИ ШАРОИТИДА АРТЕРИАЛ ГИПОТЕНЗИЯ ШАКЛЛАНИШИНИНГ ХАТАР ОМИЛЛАРИГА БОҒЛИҚЛИГИ ДАРАЖАСИ ҚИЁСИЙ ТАВСИФИ //УЗБЕКИСТОН КАРДИОЛОГИЯСИ. – 2019.

12. Sherali K., Zebiniso L., Gulbahor K. Features Of Anthropometric Indicators Of Children Of The First Year Of Life Born Of Mothers In The State Of Hypothyrozis //The American Journal of Medical Sciences and Pharmaceutical Research. – 2020. – Т. 2. – №. 09. – С. 64-68.
13. Kurbonova, Gulbahor Aslamovna, and Zebiniso Khidirovna Lapasova. "CURRENT VIEWS ON IRON DEFICIENCY ANAEMIA IN PATIENTS WITH CARDIOVASCULAR DISEASE." *The American Journal of Medical Sciences and Pharmaceutical Research* 4.03 (2022): 59-64.
14. Kurbonova G. A., Lapasova Z. K. CURRENT VIEWS ON IRON DEFICIENCY ANAEMIA IN PATIENTS WITH CARDIOVASCULAR DISEASE //The American Journal of Medical Sciences and Pharmaceutical Research. – 2022. – Т. 4. – №. 03. – С. 59-64.
15. Kurbonova, G. A., & Lapasova, Z. K. (2022). CURRENT VIEWS ON IRON DEFICIENCY ANAEMIA IN PATIENTS WITH CARDIOVASCULAR DISEASE. *The American Journal of Medical Sciences and Pharmaceutical Research*, *4*(03), 59-64.
16. Шодиев А. и др. К особенностям клинического течения и лечения нетравматических внутримозговых кровоизлияний у детей //Журнал проблемы биологии и медицины. – 2018. – №. 2.1 (101). – С. 128-131.
17. Шодиев, А., et al. "К особенностям клинического течения и лечения нетравматических внутримозговых кровоизлияний у детей." *Журнал проблемы биологии и медицины* 2.1 (101) (2018): 128-131.
18. Абдувалиев Ш. И., Шодиев А. Ш., Пардаева З. С. НЕКОТОРЫЕ ОСОБЕННОСТИ КЛИНИЧЕСКОГО ПРОЯВЛЕНИЯ НЕТРАВМАТИЧЕСКИХ ВНУТРИМОЗГОВЫХ КРОВОИЗЛИЯНИЙ У ДЕТЕЙ //XX ДАВИДЕНКОВСКИЕ ЧТЕНИЯ. – 2018. – С. 9-10.
19. Абдувалиев, Ш. И., А. Ш. Шодиев, and З. С. Пардаева. "НЕКОТОРЫЕ ОСОБЕННОСТИ КЛИНИЧЕСКОГО ПРОЯВЛЕНИЯ НЕТРАВМАТИЧЕСКИХ ВНУТРИМОЗГОВЫХ КРОВОИЗЛИЯНИЙ У ДЕТЕЙ." *XX ДАВИДЕНКОВСКИЕ ЧТЕНИЯ*. 2018.
20. Шодиев А. Ш., Абдувалиев Ш. И., Пардаева З. С. К ВОПРОСУ КЛИНИЧЕСКОГО ТЕЧЕНИЯ И ЛЕЧЕНИЯ НЕТРАВМАТИЧЕСКИХ ВНУТРИМОЗГОВЫХ КРОВОИЗЛИЯНИЙ У ДЕТЕЙ //XX ДАВИДЕНКОВСКИЕ ЧТЕНИЯ. – 2018. – С. 441-442.
21. Шодиев, А. Ш., Ш. И. Абдувалиев, and З. С. Пардаева. "К ВОПРОСУ КЛИНИЧЕСКОГО ТЕЧЕНИЯ И ЛЕЧЕНИЯ НЕТРАВМАТИЧЕСКИХ ВНУТРИМОЗГОВЫХ КРОВОИЗЛИЯНИЙ У ДЕТЕЙ." *XX ДАВИДЕНКОВСКИЕ ЧТЕНИЯ*. 2018.
22. Саркисова В., Абдурахманова К. Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке //Журнал вестник врача. – 2014. – Т. 1. – №. 01. – С. 163-166.
23. Саркисова, В., and К. Абдурахманова. "Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке." *Журнал вестник врача* 1.01 (2014): 163-166.
24. Саркисова, В., & Абдурахманова, К. (2014). Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке. *Журнал вестник врача*, *1*(01), 163-166.

25. Vladimirovna S. V. Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis //The Peerian Journal. – 2023. – T. 15. – C. 84-93.
26. Vladimirovna, Sarkisova Viktoriya. "Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis." *The Peerian Journal* 15 (2023): 84-93.
27. Vladimirovna, S. V. (2023). Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis. *The Peerian Journal*, *15*, 84-93.
28. Vladimirovna S. V. et al. Analysis of Women's Reproductive and Somatic Health, Hospitalized for Endometrial Hyperplasia and Uterine Bleeding //Eurasian Medical Research Periodical. – 2023. – T. 17. – C. 91-96.
29. Vladimirovna, Sarkisova Viktoriya, et al. "Analysis of Women's Reproductive and Somatic Health, Hospitalized for Endometrial Hyperplasia and Uterine Bleeding." *Eurasian Medical Research Periodical* 17 (2023): 91-96.
30. Vladimirovna, S. V., Vladimirovna, M. E., Xidirovna, L. Z., & Shaukatovna, I. M. (2023). Analysis of Women's Reproductive and Somatic Health, Hospitalized for Endometrial Hyperplasia and Uterine Bleeding. *Eurasian Medical Research Periodical*, *17*, 91-96.
31. Vladimirovna S. V. About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia //Global Scientific Review. – 2023. – T. 12. – C. 25-32.
32. Vladimirovna, Sarkisova Viktoriya. "About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia." *Global Scientific Review* 12 (2023): 25-32.
33. Vladimirovna, S. V. (2023). About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia. *Global Scientific Review*, *12*, 25-32.
34. Vladimirovna S. V. et al. Hyperplastic Processes of the Endometrium: Issues of Ethiopathogenesis, Clinic, Diagnosis, Treatment //Scholastic: Journal of Natural and Medical Education. – 2023. – T. 2. – №. 3. – C. 72-77.
35. Vladimirovna, Sarkisova Victoria, et al. "Hyperplastic Processes of the Endometrium: Issues of Ethiopathogenesis, Clinic, Diagnosis, Treatment." *Scholastic: Journal of Natural and Medical Education* 2.3 (2023): 72-77.
36. Vladimirovna, S. V., Safoyevna, K. D., Anvarovna, S. L., & Olegovna, X. R. (2023). Hyperplastic Processes of the Endometrium: Issues of Ethiopathogenesis, Clinic, Diagnosis, Treatment. *Scholastic: Journal of Natural and Medical Education*, *2*(3), 72-77.
37. Саркисова В. В. Патогенетические отношения артериальной гипертензии и сопротивления инсулина //IQRO JURNALI. – 2023. – Т. 2. – №. 1. – С. 727-731.
38. Саркисова, Виктория Владимировна. "Патогенетические отношения артериальной гипертензии и сопротивления инсулина." *IQRO JURNALI* 2.1 (2023): 727-731.
39. Саркисова, В. В. (2023). Патогенетические отношения артериальной гипертензии и сопротивления инсулина. *IQRO JURNALI*, *2*(1), 727-731.
40. Vladimirovna S. V. PATHOGENETIC RELATIONSHIPS OF ARTERIAL HYPERTENSION AND INSULIN RESISTANCE //IQRO JURNALI. – 2023. – T. 2. – №. 1. – C. 685-691.
41. Vladimirovna, Sarkisova Victoria. "PATHOGENETIC RELATIONSHIPS OF ARTERIAL HYPERTENSION AND INSULIN RESISTANCE." *IQRO JURNALI* 2.1 (2023): 685-691.

42. Vladimirovna, S. V. (2023). PATHOGENETIC RELATIONSHIPS OF ARTERIAL HYPERTENSION AND INSULIN RESISTANCE. *IQRO JURNALI*, *2*(1), 685-691.
43. Vladimirovna S. V. ABOUT THE CAUSES OF ENDOMETRIAL HYPERPLASIA AND FORMS OF ENDOMETRIAL HYPERPLASIA //ResearchJet Journal of Analysis and Inventions. – 2022. – Т. 3. – №. 11. – С. 66-72.
44. Vladimirovna, Sarkisova Victoria. "ABOUT THE CAUSES OF ENDOMETRIAL HYPERPLASIA AND FORMS OF ENDOMETRIAL HYPERPLASIA." *ResearchJet Journal of Analysis and Inventions* 3.11 (2022): 66-72.
45. Vladimirovna, S. V. (2022). ABOUT THE CAUSES OF ENDOMETRIAL HYPERPLASIA AND FORMS OF ENDOMETRIAL HYPERPLASIA. *ResearchJet Journal of Analysis and Inventions*, *3*(11), 66-72.
46. Vladimirovna S. V. et al. Adenomyosis as an Independent Unit of Dysfunction of the Endometrium and Uterine Myometrium //Scholastic: Journal of Natural and Medical Education. – 2023. – Т. 2. – №. 3. – С. 85-91.
47. Vladimirovna, Sarkisova Victoria, et al. "Adenomyosis as an Independent Unit of Dysfunction of the Endometrium and Uterine Myometrium." *Scholastic: Journal of Natural and Medical Education* 2.3 (2023): 85-91.
48. Vladimirovna, S. V., Shoukatovna, I. M., Ulugbekovna, R. F., & Olegovna, X. R. (2023). Adenomyosis as an Independent Unit of Dysfunction of the Endometrium and Uterine Myometrium. *Scholastic: Journal of Natural and Medical Education*, *2*(3), 85-91.
49. Sarkisova V. et al. UTERINE ARTERY EMBOLIZATION AS A METHOD OF TREATMENT OF UTERINE FIBROIDS //Science and innovation. – 2023. – Т. 2. – №. D3. – С. 115-121.
50. Sarkisova, V., et al. "UTERINE ARTERY EMBOLIZATION AS A METHOD OF TREATMENT OF UTERINE FIBROIDS." *Science and innovation* 2.D3 (2023): 115-121.
51. Sarkisova, V., Muradova, E., Saurabh, S., & Sarang, M. (2023). UTERINE ARTERY EMBOLIZATION AS A METHOD OF TREATMENT OF UTERINE FIBROIDS. *Science and innovation*, *2*(D3), 115-121.