MOLECULAR-GENETIC ASPECTS OF KABUKI MAKEUP SYNDROME. Review

1Lastivka I.V. https://orcid.org/0000-0002-9088-1301
2Antsupva V.V. https://orcid.org/0000-0002-7849-2602
3Babintseva A.H. https://orcid.org/0000-0002-3859-6431
4Unhuriyan M.D. https://orcid.org/0000-0002-8385-6176
2Ushko LA https://orcid.org/0000-0003-3017-7766

1Bukovinian State Medical University, Chernivtsi, Ukraine
2Bogomolets National Medical University, Kyiv, Ukraine
3Chernivtsi Regional Perinatal Center, Chernivtsi, Ukraine

Relevance. Kabuki Makeup Syndrome (KS) is a rare monogenic genetic disease characterized by multiple malformations. The phenotype includes specific facial features, skeletal and dermato-glyphic abnormalities, mental retardation, short stature. Most cases are associated with de novo mutations in the KMT2D and KDM6A genes. However, in 25% of patients with KS, the genetic basis remains unknown, which indicates the genetic heterogeneity of the disease and encourages further accumulation of clinical experience in KS. The article summarizes current data on the molecular genetic aspects of the development of Kabuki Makeup Syndrome and describes its own clinical case of Kabuki Makeup Syndrome Type I.

Objective: to summarize the data on modern molecular-genetic aspects of the development of Kabuki makeup syndrome on the example of a clinical case.

Materials and methods. Analysis of scientific publications in the international electronic scientometric database Scopus, PubMed by keywords. Search depth – 15 years (2007-2021). The clinical case of Kabuki Makeup Syndrome from our own practice. Clinical and genealogical, molecular-genetic, cytogenetic, instrumental research methods.

Results. According to current data, the development of Kabuki Makeup Syndrome is due to mutations in the KMT2D (MLL2) gene, which belongs to the genes that control embryogenesis. KMT2D functions as a promoter of the expression of other genes and the KDM6A gene; encodes a large multia domain protein that interacts with the SET1/COMPASS complex. KDM6A is a cofactor physically associated with the KMT2D-COMPASS complex and exhibits demethylase activity in histone 3. Gene mutations KMT2D and KDM6A associated with KS lead to a lack of functioning of the corresponding enzyme, which leads to impaired methylation of histones and active genes in many organs and tissues of the body. Depending on the type of mutation in the KMT2D and KDM6A genes, there are two types of Kabuki Makeup Syndrome. KS type 1 with autosomal dominant type of inheritance due to pathogenic mutations in the KMT2D gene in a heterozygous state on chromosome 12q13.12. 70% of patients have KS1. Type 2 KS is an X-linked disease that develops as a result of a heterozygous pathogenic mutation in the KDM6 gene. In most cases, KS mutations are sporadic, but families with parent-to-child transmission have been described. In patients with phenotypic signs of KS pathogenic mutations are detected in 75% of cases. Pathogenic mutations in the KMT2D gene can be detected in mosaic form, and the carrier can pass this mutation on to offspring. Pathogenic mutations have not been described in phenotypically healthy people.

Here is our own observation. The girl with a combined congenital heart defect and multiple stigmas of dysembryogenesis was born at 36 weeks with a weight of 2930, 49 cm long, on the Apgar scale 8/8 points from the three planned pregnancy in parents who already had an older healthy boy. In connection with multiple malformations, the girl underwent a syndromic diagnosis using the program «Face2gene»; Kabuki Makeup Syndrome is suspected. Molecular genetic analysis revealed a pathogenic mutation (c.11884C>T) (p.Gln3962*) in the KMT2D gene, which is associated with autosomal dominant Kabuki Makeup Syndrome of type 1 (MedGen UID: 893727).

Conclusions. Kabuki Makeup Syndrome has clinical and molecular polymorphisms. Most of the registered KMT2D mutations occur de novo and occur in episodic cases. The described case demonstrates the molecular-positive Kabuki Makeup Syndrome of type I. The identified variant c.11884C>T(p.Gln3962*) in the KMT2D gene is associated with the autosomal dominant Kabuki Makeup Syndrome (MedGen UID: 893727). Verification of the diagnosis of the disease and prevention of KS in siblings is based on the results of molecular genetic analysis. The prognosis of this disease depends on the severity of heart disease and intellectual impairment. Early diagnosis determines the type and timing of therapeutic interventions, is crucial for medical and genetic counseling of the family.

Key words: Kabuki Makeup Syndrome, specific facial features, KMT2D and KDM6A genes mutations.
Pathogenic and non-pathogenic mutations in the \textit{KMT2D} and \textit{KDM6A} genes have been described in the literature [3]. In patients with phenotypic signs of KS pathogenic mutations are detected in 75\% of cases. Pathogenic mutations have not been described in phenotypically healthy people. Small deletions or insertions, nonsense and missense mutations, shift of the reading frame are described as the reason of development of the disease, some of them are pathogenic, some of them are of unknown clinical significance. In 25\% of patients with KS, the genetic basis remains unknown, which indicates the genetic heterogeneity of the disease and encourages further accumulation of clinical experience [4-8].

\textbf{Objective:} to summarize the data on modern molecular-genetic aspects of the development of Kabuki makeup syndrome on the example of a clinical case.

\section*{MATERIALS AND METHODS}

Analysis of scientific publications in the international electronic scientometric database Scopus, PubMed by keywords. Search depth – 15 years (2007-2021). The clinical case of Kabuki Makeup Syndrome from our own practice. Clinical and genealogical, molecular-genetic, cytogenetic, instrumental research methods.

\section*{RESULTS AND DISCUSSION}

According to current research, the etiopathogenesis of the disease is associated with mutations in the \textit{KMT2D} gene (also known as \textit{MLL2}), which belongs to the family of mixed-cell leukemia genes required for embryogenesis and functions as a promoter of other genes and the \textit{KDM6A} gene. \textit{KMT2D} encodes a large multidomain protein that interacts with the \textit{SET1/COMPASS} complex. \textit{KDM6A} is a cofactor physically associated with the \textit{KMT2D-COMPASS} complex and exhibits demethylase activity in histone 3. Together, the components of the \textit{KMT2D-COMPASS} complex remove inhibitory epigenetic labels and add activating labels, namely mono-, di- or trimethylation of histone 3. Depending on the type of mutation in the genes that cause KS, there are two types: KS type 1 with autosomal dominant (AD) type of inheritance, which is caused by heterozygous pathogenic mutations in the \textit{KMT2D} gene on chromosome 12q13.12 and KS type 2 – X-linked disease that develops as a result of a heterozygous pathogenic mutation in the KDM6 gene. In most patients (70\%) register KS1. Gene mutations \textit{KMT2D} and \textit{KDM6A} associated with KS, lead to a lack of functioning of the corresponding enzyme, which leads to impaired methylation of histones and activation of specific genes in many organs and tissues of the body. In most cases, KS mutations are sporadic, but families with parent-to-child transmission have been described. Pathogenic mutations in the \textit{KMT2D} gene can be detected in a mosaic form, and the carrier can pass this mutation to offspring [4, 5, 8-11].

Various cytogenetic abnormalities have been described in patients with clinically established KS, which includes an annular X chromosome, translocations, inversions, duplications [8, 10, 11].

At KS there are mutations-negative and mutations-positive patients. Phenotypic signs of the disease in mutation-negative and mutation-positive patients do not different [4, 8, 10, 11].

The phenotype of children with KS includes microcephaly, arched eyebrows with thickening to the center/thinning of the lateral part, wide nose, hypertelorism, elongated eye slits, antimongoloid incision of the eyes, long thick eyelashes, ectropion of the lateral part of the lower eyelid and short, short low-set auricles, micrognathia, thin upper lip, gothic palate and/or cleft palate, abnormalities of the teeth with the formation of a false bite, low hair growth on the back of the head, hyperelastic skin, hirsutism, skin pigmentation disorders, nail dysplasia [1-3, 6].

Among the skeletal anomalies in KS, the most common are anomalies of the sutures of the skull, spine and vertebrae, shoulders and ribs, hands, dislocations/subdislocations of the joints. KS is characterized by postnatal growth retardation that develops during the first years of life. By 6-10 years, some patients develop obesity. Delayed speech development in patients with KS occurs in 100\% of cases. Intellectual deficit from mild to moderate. Cases of autism-like behavior in children with KS have been described. Among neurologic displays muscular hypotension, coordinating disturbances, a delay of development of stato-kinetic skills can be observed. Neuroimaging reveals ventriculodilation of the lateral ventricles, hypoplasia of the corpus callosum, hypoplasia of the adenohipophysis. Seizures occur in 36-45\% of cases at any age, more often in girls. Ophthalmic findings include ptosis, strabismus, nystagmus, paralysis of the afferent nerve, microphthalmia. Features of dermatoglyphics – high fetal pads on the fingertips, increasing the ulnar radius, increasing the radius of the hypotenuse, the absence of the finger triradius – the only difficult on the palm. With corticosteroids can be defects of the kidneys and urinary tract, genitals, gastrointestinal tract, ENT organs, cardiovascular system, various hernias. In 40-50\% of cases, congenital heart defects (CHD) are diagnosed (defects in the valves or membranes of the heart, coarctation of the aorta, transposition of large vessels). Children with SK are prone to bronchopulmonary diseases with a prolonged course. Endocrine pathology is represented by hypothyroidism, diabetes, hypoglycemia or diabetes mellitus, late puberty, pituitary dwarfism. At KS the immune status is broken. There is a decrease in serum immunoglobulin classes (80\% – IgA deficiency), due to the fact that the genes \textit{KMT2D} and \textit{KDM6A} are involved in epigenetic regulation and affect the development of immunocompetent cells [1-3, 6-9].

Here is our own observation of early diagnosis of KS in a child. Girl O., born in 2019, was born from the third
MOLECULAR-GENETIC ASPECTS OF KABUKI MAKEUP SYNDROME. REVIEW

desired and planned pregnancy, which took place against the background of the threat of miscarriage, polyhydramnios, hypothyroidism. The older brother is healthy from the first pregnancy. The second pregnancy ended in miscarriage in early pregnancy. The third pregnancy occurred against the background of drugs that promote conception. ATC in the fetus was diagnosed at 20 weeks of gestation.

Heredity through the mother is burdened with cardiovascular and oncopathological pathology; great-grandmother on the mother’s line suffers from diabetes. Heredity on the paternal line is burdened by oncopathology; grandfather suffers from diabetes. Both parents suffer from hypothyroidism.

The baby was born at 36 weeks of gestation with a weight of 2930, length 49 cm, Apgar scale 8/8 points. Due to severe congenital heart disease (CHD), immediately after birth, the child was transferred to the Department of Pediatric Cardiology and Cardiac Surgery in Kyiv for examination and surgical treatment. Parents refused surgical treatment after reviewing the possible risks of surgical treatment and long-term prognosis. The child was transferred to the neonatal pathology department in Chernivtsi. The condition on admission was considered severe, which was due to the combined CHD and feeding problems. She was fed through a tube. Reflexes are suppressed, the tone of muscles is lowered. Heart tones are rhythmic, loud, systolic murmur along the left edge of the sternum. The abdomen is soft, painless on palpation. The liver protrudes 2 cm from under the costal arch. Defecation without abnormalities.

The child was consulted by a geneticist, revealed multiple developmental abnormalities (CHD, cleft palate, protruding ear shells, arched eyebrows, long oblique eye slits, blue sclera, epicanthus, ectropion of the lower eyelids, wide tip of the nose, hand, hypothyroidism), dysplasia of the hip joints, muscular hypotension, delayed stato-kinetic development. Syndromological diagnostics was performed using the diagnostic program «Face2gene»; Kabuki Makeup Syndrome is suspected; molecular genetic testing is recommended to verify the diagnosis. Molecular genetic analysis revealed a pathogenic mutation (c.11884C>T(p.Gln3962*) in the KMT2D gene, which is associated with autosomal dominant Kabuka makeup syndrome (MedGen UID: 893727). The identified variant c.11884C>T(p.Gln3962*) in the KMT2D gene is associated with the autosomal dominant Kabuka makeup syndrome (MedGen UID: 893727). Verification of the diagnosis of the disease and prevention of KS in siblings is based on the results of molecular genetic analysis. The prognosis of this disease depends on the severity of heart disease and intellectual impairment. Early diagnosis determines the type and timing of therapeutic interventions, is crucial for medical and genetic counseling of the family.

CONCLUSIONS

Kabuki Makeup Syndrome has clinical and molecular polymorphisms. Most of the registered KMT2D mutations occur de novo and occur in episodic cases. The described case demonstrates the molecular-positive Kabuki Makeup Syndrome of type I. The identified variant c.11884C>T(p.Gln3962*) in the KMT2D gene is associated with the autosomal dominant Kabuka makeup syndrome (MedGen UID: 893727). Verification of the diagnosis of the disease and prevention of KS in siblings is based on the results of molecular genetic analysis. The prognosis of this disease depends on the severity of heart disease and intellectual impairment. Early diagnosis determines the type and timing of therapeutic interventions, is crucial for medical and genetic counseling of the family.

REFERENCES

1. Jones KL. Smith’s recognizable patterns of human malformation, 8th edition. Elsevier, 2021. 1088 p. View at: Scopus: https://www.elsevier.com/books/smiths-recognizable-patterns-of-human-malformation/jones/978-0-323-63882-1
2. Kozlova SI, Demikova NS. Hereditary syndromes and medical genetic counseling, 3th edition. KMK Scientific Publishing Partnership, 2007; 447: 93-94. View at: Publisher Site: https://medkniga.com.ua/15726-nasledstvennie-sindromi-i-mediiko-geneticheskoe-konsultirovanie-atlas-spravochnik-3-e-izd/
3. Kabuki syndrome-1. OMIM: 147920. Mendelian inheritance in humans online. McKusick-Nathans Institute of Genetic Medicine, John Hopkins University, National Center for Biotechnology Information. National Medical Library. View at: Publisher Site: https://www.omim.org/entry/147920?search=Kabuki&highlight=kabuki
4. Maas NMC, Van de Putte T, Melotte C, Francis A, Schrander-Stumpel C, Sanlaville D, Genevieve D, Lyonnet S, Dimitrov B, Devriendt K, Fryns J-P, Vermeesch JR. The C20or133 gene is disrupted in a patient with Kabuki syndrome. J Med Genet. 2007;44(9):562-9. DOI: 10.1136/jmg.2007.049510 View at: Publisher Site: https://jmg.bmj.com/content/44/9/562
PubMed: https://pubmed.ncbi.nlm.nih.gov/17586838/
PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2597955/
5. Zarate YA, Zhan H, Jones JR. Inrequent Manifestations of Kabuki Syndrome in a Patient with Novel MLL2 Mutation. Mol Syndromol. 2012;3(4):180-184 DOI: 10.1159/000342253 View at: Publisher Site: https://www.karger.com/Article/FullText/342253
PubMed: https://pubmed.ncbi.nlm.nih.gov/23239960/
PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3507269/
6. Carosso GA, Boukas L, Augustin JJ, Nguyen HN, Winer BL, Cannon GH, Robertson JD, Zhang L,
**Молекулярно-генетичные аспекты синдрома Гриму Кабукі. Огляд**

1. Lastivka I.V., Antsupov V.V., Babintseva A.H., Unhurian M.D., Ushko I.A.

**Актуальность.** Синдром Гриму Кабукі (КС) – это редкое наследственное генетическое заболевание, характеризующееся множественными вадами развития. Фенотип включает специфичные риски обличий, скелетные и дерматоглифические отклонения, низкий рост. Более 90% вкладчиков связаны с мутациями в генах KMT2D и KDM6A. Однако у 25% пациентов с КС генетическая основа неизвестна, что свидетельствует о генетической гетерогенности заболевания.

**Цель:** узаконить данные о молекулярно-генетических аспектах развития синдрома Гриму Кабукі на прикладі клінічного випадку.

**Материалы и методы.** Анализ публикаций с международных наукометрических журналов, включая Scopus и PubMed, за ключевыми словами. Глобина пошук — 15 років (2007-2021). Клинический вклад синдрому Гриму Кабукі по сравнению с другими заболеваниями.

**Результаты.** Синдром Гриму Кабукі — редкое наследственное генетическое заболевание, характеризующееся множественными вадами развития. Фенотип включает специфичные риски обличий, скелетные и дерматоглифические отклонения, низкий рост. Более 90% вкладчиков связаны с мутациями в генах KMT2D и KDM6A. Однако у 25% пациентов с КС генетическая основа неизвестна, что свидетельствует о генетической гетерогенности заболевания.

**Заключение.** Синдром Гриму Кабукі — редкое наследственное генетическое заболевание, характеризующееся множественными вадами развития. Фенотип включает специфичные риски обличий, скелетные и дерматоглифические отклонения, низкий рост. Более 90% вкладчиков связаны с мутациями в генах KMT2D и KDM6A. Однако у 25% пациентов с КС генетическая основа неизвестна, что свидетельствует о генетической гетерогенности заболевания.

**Аннотация:** Синдром Гриму Кабукі (КС) – редкое наследственное генетическое заболевание, характеризующееся множественными вадами развития. Фенотип включает специфичные риски обличий, скелетные и дерматоглифические отклонения, низкий рост. Более 90% вкладчиков связаны с мутациями в генах KMT2D и KDM6A. Однако у 25% пациентов с КС генетическая основа неизвестна, что свидетельствует о генетической гетерогенности заболевания.

**Ключевые слова:** синдром Гриму Кабукі, КС, генетические аспекты, фенотип, вкладанный вклад.
активации специфичных генов у багатьох органах та тканинах організму. Залежно від виду мутацій в генах KMT2D та KMD6A, виділяють два типи синдрому грима Кабуки. КС 1-го типу з аутосомно-домінантним типом успадкування, обумовлений патогенними мутаціями в гені KMT2D в гетерозиготному стані на хромосомі 12q13.12. У 70 % хворих виявляють KС1. КС 2-го типу – Х-сцеплене захворювання, що розвивається в результаті гетерозиготної патогенної мутації в гені KDM6A. У більшості випадків КС мутації є спорадичними, однак описані родини з передачею захворювання від батьків до дітей. У хворих з фенотиповими ознаками KС патогенні мутації виявлені в 75 % випадків. Патогенні мутації в гені KMT2D можуть бути виявлені в мозаїчній формі, а носій може передати цю мутацію нащадкам. Патогенні мутації не описані у фенотипово здорових людей.

Виділення специфічних рис у дітей з синдромом грима Кабуки (MedGen UID: 893727). Відомо, що у носіїв можуть бути виявлені в мозаїчній формі, а носій може передати цю мутацію нащадкам. Патогенні мутації не описані у фенотипово здорових людей.

Синдром грима Кабуки має клинічний та молекулярний полиморфізм. Більшість із зареєстрованих мутацій KMT2D викликують де-ноо і зустрічаються в епізодичних випадках. Описаний випадок демонструє молекулярно-позитивний синдром грима Кабукі I типу. Ідентифікований варіант c.11884C>T(gln3962*) у гені KMT2D асоціюється з аутосомно-домінантним синдромом грима Кабуки (MedGen UID: 893727). Верифікація діагнозу захворювання та профілактика KС у сібсів проводиться на основі результатів молекулярно-генетичного аналізу. Прогноз захворювання при цій патології залежить від тяжкості уражень, серед них значною ролю відіграє інтелект.

Актуальність. Синдром грима Кабуки (КС) – це редке мононгенне генетичне заболювання, характеризуючеся множественными пороками розвитку. Більшість хворих відноситься до генів KMT2D і KMD6A, вірогідно, що вони виконують схожі функції в клітині.

Результати. По современным данным, развитие синдрома грима Кабуки обусловлено мутациями генов KMT2D (MLL2), который относится к генам, контролирующим эмбриогенез. KMT2D функционирует как промотор экспрессии других генов, кодирующих белки, вовлеченные в процесс SET1/COMPASS. KMD6A является кофактором, физически связанным с комплексом KMT2D-COMPASS, и проявляет деметилазную активность в гистоне 3. Гены KMT2D и KMD6A, связанные с КС, что приводит к нарушению метилирования гистонов и активации специфических генов во многих органах и тканях организма. В зависимости от вида мутации в генах KMT2D и KMD6A, выделяют два типа синдрома грима Кабуки. KС 1-го типа с аутосомно-домінантным типом наследования, обусловлен патогенными мутациями в гені KMT2D в гетерозиготном состоянии на хромосоме 12q13.12. У 70 % больных обнаруживают KС1. KС 2-го типа – Х-сцепленное заболевание, развивающееся в результате гетерозиготной патогенной мутации в гені KMD6A. В большинстве случаев КС мутации являются спорадическими, однако описаны семьи с передачей заболевания от родителей к детям. У больных с фенотипическими признаками КС патогенные мутации могут быть обнаружены в мозаичной форме, а носитель может передать эту мутацию потомкам. Патогенные мутации не описаны у фенотипически здоровых людей.

Приводимое специфическое наблюдение. Девочка с комбинированным врожденным пороком сердца и множественными стигмами грима Кабуки из собственной практики. Девочка родилась с множественными пороками развития сердца и специфическими чертами лица. У девочки была проведена синдромологическая диагностика с помощью программы «Face2gene»; заподозрено синдром грима Кабуки. Молекулярно-генетический анализ выявил патогенную мутацию (c.11884C>T(gln3962*) в гені KMT2D, которая ассоциируется с аутосомно-домінантним вариантом грима Кабуки 1 типа (MedGen UID: 893727). Верификация диагноза заболевания и профилактика KС у сібсів проводиться на основі результатів молекулярно-генетичного аналізу. Прогноз захворювання при цій патології залежить від тяжкості уражень, серед них значною ролю відіграє інтелект.

Выводы. Синдром грима Кабуки имеет клинический и молекулярный полиморфизм. Большинство из зарегистрированных мутаций KMT2D возникают de novo и встречаются в эпизодических случаях. Описанный случай демонстрирует молекулярно-полиморфный синдром грима Кабуки, специфические черты лица, мутации генов KMT2D и KMD6A.

Ключевые слова: синдром грима Кабуки, специфичні риси обличчя, мутації генів KMT2D, KMD6A.