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MOLECULAR DIAGNOSTICS IN RETINOBLASTOMA (REVIEW)

Resume: *This review of the literature considers current literature data on new biomarkers of retinoblastoma (RB) and their clinical application, as well as issues from areas such as epigenetics, proteomics and radiogenomics and clinically significant aspects of genetic testing and genetic counseling for a child with retinoblastoma.*
Purpose: *study of the molecular genetic features of retinoblastoma based on modern biomarkers of RP based on the results of materials from domestic and foreign experience.*
Materials and methods: *Research publications were searched and analyzed in databases and web resources Web of Science, MEDLINE, PubMed, Google Scholar, Springer and e-library, using the keywords: retinoblastoma, RB1 gene, molecular diagnostics, genetic biomarkers, epigenetics, proteomics, radiogenomics. Of all the selected articles for further analysis, 53 sources were included that corresponded to the objectives of our study.*
Results and conclusions: *Molecular genetic study of structural damage to the RB1 gene in RD is necessary to confirm or exclude the hereditary nature of the disease, which will allow choosing an adequate algorithm for monitoring and treating the tumor, as well as planning further childbearing. In the hereditary form of RB, the RB1 gene is damaged in all somatic cells: patients have a high risk of developing other tumors of various localization. Timely and modern schemes of combined treatment allow preserving the eye and visual functions of patients, which is possible only if the diagnosis is made early, the methods of treatment that are effective and least dangerous for the child are qualified and adequate. This prompts the search for new approaches to improve the early diagnosis of RB. Patients with a hereditary form of RB require regular monitoring in oncological dispensaries, and timely molecular diagnosis of damage to the RB1 gene becomes a top priority.*
Conclusion: *Thus, the analysis provides useful information about new biomarkers of RP that can be used in diagnosis, as prognostic indicators, and may contribute to understanding the pathogenesis of RP and help determine specific treatment strategies. Identification of the genetic factors underlying these effects will not only provide a more accurate prognosis, but may also point to mechanisms that can be used to reduce the risk of tumor development. New international prospective multicentre studies and the search for blood biomarkers that can predict the risk of micrometastasis may contribute to better patient stratification.*
Keywords: *retinoblastoma, RB1 gene, molecular diagnostics, genetic biomarkers, epigenetics, proteomics, radiogenomics.*

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РЕТИНОБЛАСТОМАНЫҢ МОЛЕКУЛЯРЛЫҚ ДИАГНОСТИКАСЫ (ӘДЕБИ ШОЛУ)

Түйін: Әдебиеттің бұл шолуы ретинобластоманың (RB) жаңа биомаркерлері және олардың клиникалық қолданылуы, сондай-ақ эпигенетика, протеомика және радиогеномика сияқты сала-

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МОЛЕКУЛЯРНАЯ ДИАГНОСТИКА ПРИ РЕТИНОБЛАСТОМЕ (ОБЗОР ЛИТЕРАТУРЫ)

Резюме: В представленном обзоре литературы рассматриваются современные литературные данные о новых биомарке-

лардағы мәселелер және ретинобластомамен ауыратын балаға генетикалық тестілеудің және генетикалық кеңес берудің клиникалық маңызды аспектілері бойынша ағымдағы әдебиет деректерін қарастырады. .

Мақсаты: отандық және шетелдік тәжірибеден алынған материалдардың нәтижелері негізінде, заманауи биомаркерлері негізінде ретинобластоманың молекулалық-генетикалық ерекшеліктерін зерттеу.

Материалдар мен әдістер: Ретинобластома, RB1 гені, молекулалық диагностика, генетикалық биомаркерлер, эпигенетика, протеомика сияқты түйінді сөздерді қолдану арқылы Web of Science, MEDLINE, PubMed, Google Scholar, Springer және e-library дерекқорлары мен веб-ресурстарында зерттеу жарияланымдары іздестірілді және талданды. , радиогеномика. Әрі қарай талдау үшін барлық таңдалған мақалалардың ішінен зерттеу мақсатына сәйкес келетін 53 дереккөз қосылды.

Нәтижелер мен қорытындылар: РБ-дағы RB1 генінің құрылымдық зақымдануын молекулярлық-генетикалық зерттеу аурудың тұқым қуалайтын сипатын растау немесе жоққа шығару үшін қажет, бұл ісіктерді бақылау мен емдеудің барабар алгоритмін таңдауға, сондай-ақ одан әрі бала тууды жоспарлауға мүмкіндік береді. RB тұқым қуалайтын түрінде RB1 гені барлық соматикалық жасушаларда зақымдалған: науқастарда әртүрлі локализацияның басқа ісіктерінің даму қаупі жоғары. Біріктірілген емдеудің уақтылы және заманауи схемалары пациенттердің көз және көру функцияларын сақтауға мүмкіндік береді, бұл диагноз ерте қойылған жағдайда ғана мүмкін болады, бала үшін тиімді және ең қауіпті емес емдеу әдістері білікті және барабар. Бұл РБ ерте диагностикасын жақсартудың жаңа тәсілдерін іздестіруге итермелейді.РБ тұқым қуалайтын түрімен ауыратын науқастар онкологиялық диспансерлерде тұрақты бақылауды қажет етеді, ал RB1 генінің зақымдалуын уақтылы молекулярлық диагностикалау басты басымдыққа айналады.

Қорытынды: Осылайша, талдау болжамдық индикаторлар ретінде диагностикада пайдаланылуы мүмкін РБ-ның жаңа биомаркерлері туралы пайдалы ақпарат береді және РТ патогенезін түсінуге ықпал етеді және нақты емдеу стратегияларын анықтауға көмектеседі. Бұл әсерлердің негізінде жатқан генетикалық факторларды анықтау дәлірек болжамды қамтамасыз етіп қана қоймайды, сонымен қатар ісіктердің даму қаупін азайту үшін қолданылатын механизмдерді де көрсетуі мүмкін. Жаңа халықаралық перспективалық көп орталықты зерттеулер және микрометастаз қаупін болжай алатын қан биомаркерлерін іздеу пациенттердің стратификациясын жақсартуға ықпал етуі мүмкін.

Түйінді сөздер: ретинобластома, RB1 гені, молекулалық диагностика, генетикалық биомаркерлер, эпигенетика, протеомика, радиогеномика.

рах ретинобластомы(РБ) и их клинического применения, а также проблемы из таких областей, как эпигенетика, протеомика и радиогеномика и клинически значимые аспекты генетического тестирования и генетического консультирования для ребенка с ретинобластомой.

Цель: изучение молекулярно-генетических особенностей ретинобластомы на основе современных биомаркеров РБ по результатам материалов отечественного и зарубежного опыта.

Материалы и методы: Проведен поиск и анализ научных публикаций в базах данных и веб-ресурсах Web of Science, MEDLINE, PubMed, Google Scholar, Springer и e-library, по ключевым словам: ретинобластома, ген RB1, молекулярная диагностика, генетическое биомаркеры, эпигенетика, протеомика, радиогеномика. Из всех отобранных статей для последующего анализа было включено 53 источника, соответствующих целям нашего исследования.

Результаты и выводы: Молекулярно-генетическое исследование структурных повреждений гена RB1 при РБ необходимо для подтверждения или исключения наследственного характера заболевания, что позволит выбрать адекватный алгоритм наблюдения и лечения опухоли, а также планировать дальнейшее деторождение. При наследственной форме РБ ген RB1 поврежден во всех соматических клетках: у пациентов существует высокий риск развития других опухолей различной локализации. Своевременные и современные схемы комбинированного лечения позволяют сохранить глаз и зрительные функции пациентам, что возможно только при условии ранней постановки диагноза, квалифицированного и адекватного использования эффективных и наименее опасных для ребёнка методов лечения. Это побуждает к поиску новых подходов для совершенствования ранней диагностики РБ.За больным с наследственной формой РБ необходимо регулярное наблюдение в онкологических диспансерах, а своевременная молекулярная диагностика повреждений гена RB1 становится первоочередной задачей.

Заключение: Таким образом анализ дает полезную информацию о новых биомаркерах РБ, которые могут быть использованы в диагностике, в качестве прогностических индикаторов и могут способствовать пониманию патогенеза РБ и помочь определить конкретные стратегии лечения. Идентификация генетических факторов, лежащих в основе этих эффектов, не только поможет получить более точный прогноз, но также может указать на механизмы, которые могут быть использованы для снижения риска развития опухоли.

Новые международные проспективные многоцентровые исследования и поиск биомаркеров крови, которые могут предсказать риск микрометастазирования, могут способствовать лучшей стратификации пациентов.

Ключевые слова: ретинобластома, ген RB1, молекулярная диагностика, генетическое биомаркеры, эпигенетика, протеомика, радиогеномика.

Introduction. Retinoblastoma (RB) is the most common intraocular malignancy in childhood and can affect one or both eyes. It is usually caused by a biallelic mutation of the RB1 tumor suppressor gene, leading to malignant transformation of primitive retinal cells. Mutations in both RB1 alleles in the retinal progenitor cell are significant, with one mutation being either germline or somatic and the other always somatic[1].

Identification of a patient's RB1 germline status allows differentiation between hereditary and sporadic variants of retinoblastoma. All patients with bilateral retinoblastoma are hereditary. Non-hereditary retinoblastoma is always unilateral, with 98% being caused by the loss of both RB1 alleles from the tumor, while 2% have normal RB1 in tumors initiated by amplification of the MYCN oncogene[2]. A good understanding of the genetics of retinoblastoma is critical to assessing the short-term (risk of additional tumors in the same eye and the other eye) and long-term prognosis and suggesting cost-effective surveillance strategies. Although many studies have investigated the pathogenesis of RP, there is a lack of full understanding of these mechanisms associated with cellular and molecular targets.Diagnosis of retinoblastoma in children is one of the most difficult problems in pediatric ophthalmology, due to the variety of types of tumor growth and the similarity of the clinical diagnostic picture with diseases that mimic RB. With timely detection of RB, the survival rate of affected children is more than 95% [3]. Globally, mortality is significantly higher due to late diagnosis, poor access to multidisciplinary retinoblastoma-specific medical care, lack of genetic testing and counseling, and socioeconomic factors.A variety of diagnostic approaches and related clinical treatments have been developed to improve clinical outcomes. However, there are limitations when using modern methods. Recently, many studies have identified new biomarkers of RB that can be used in diagnosis, as prognostic indicators, and may contribute to understanding the pathogenesis of RB and help determine specific treatment strategies. Identification of the genetic factors underlying these effects will not only lead to a more accurate prognosis, but may also point to mechanisms that can be used to reduce the risk of developing a tumor. Retinoblastoma , as a tumor of the retina of neuroectodermal origin, develops in utero or at an early age and is characterized by a high degree of malignancy, invasiveness, and the ability to quickly metastasize to neighboring organs and tissues. The proportion of RB among all malignant tumors in children is 6% and 90-95% of all malignant tumors of the eye. In recent years, there has been an increase in the frequency of RB in the population: currently it is 1:15000-18000 live newborns worldwide [1], although 20 years ago the incidence of the tumor was estimated as 1:30000 [4]. Retinoblastoma is the prototype of genetic cancer [5]. The tumors have a mutation in both copies of the RB1 tumor suppressor gene, located on the long arm of chromosome 13 (13q14), which codes for the retinoblastoma protein (pRB). The tumor is initiated through a biallelic loss of the tumor suppressor gene RB1 in more than 95% of cases [1] and develops after additional genetic/epigenetic changes [1,6,7]. RB can occur either sporadically or as a hereditary disease (Knudson, 1971) [6]. Hereditary RB accounts for 40% of all cases, of which 80% are bilateral, 15% unilateral, and 5% trilateral (bilateral retinoblastoma with pineal/midline neuroectodermal tumor). In about 60% of cases, it is non-hereditary RB, which is always unilateral [5].

Main part. The etiology of hereditary and most non-hereditary forms of RB is caused by a mutation of the oncosuppressor gene RB1, localized on the long arm of chromosome 13 (13q14.2) [8].The hereditary mutation RB1 is transmitted in an autosomal dominant manner [9]. This predisposition may be passed on by the parent carrying the mutation (family forms) or may occur as a de novo event. Under these conditions, retinoblastoma is usually bilateral or unilateral multifocal, and the child is at risk of developing other extraocular tumors (soft tissue sarcoma, osteosarcoma, carcinoma, high-grade glioma, malignant melanoma) [10–12].

Types of mutations. By inactivation of the RB1 gene, types of mutations are obtained:

- chromosomal, penetrating into the areas of detection of the RB1 gene on the long arm of chromosome 13q14.2 (interstitial, terminal deletions),
- genes that change the DNA structure of the RB1 gene,
- epigenetic, leading to impaired gene function with a preserved structure (due to impaired methylation, changes in microRNA expression).

The above mutations in rare cases can be of a mosaic nature, occur at the early stages of p ostzygotic recombinations in the development of the embryo, which require additional high-resolution techniques for their diagnosis. According to the literature data, mosaic mutations in the RB1 gene occur with a frequency of 5.5 and 3.8% in bilateral and monolateral RB, respectively [13, 14].

Recent studies have shown an association of non-hereditary monolateral retinoblastomas with mutations in other genes, in particular, with amplification of the MYCN gene in the presence of normal function of the RB1 gene [15, 16].

Genomic alterations in retinoblastoma are uniquewith common gains at 1q, 2p, and 6p and loss at 16q. The 6p (44–69%) or 1q (38–70%) gains are most frequently identified in tumors, followed by the 2p gain (15–43%) and 16q loss (18–46%) [17-23]. The candidate drivers are subsequently defined by minimally overlapping regions of each common gain or loss and include MDM4, KIF14 in 1q, MYCN in 2p, DEK, E2F3, ID4 and SOX4 in 6p, and CHD11 and RBL2 in 16q. Interestingly, the 1q gain and 16q loss in tumors are indicative of increased levels of genomic instability and associated with late diagnosis and non-hereditary retinoblastoma [18,19,22,24]. Recurrent loss of 16q is believed to impair candidate suppressor genes and is implicated in advanced disease [25-27]. MYCN gain/amplification occurs in approximately 8% of

retinoblastoma and is included in the most common focal genomic aberration [28,29,30]. A copy number of MYCN greater than 28 is considered high amplification and is associated with RB1+/+ or RB1+/- retinoblastoma [28,31]. High MYCN amplification is proposed as a novel mechanism of disease initiation in retinoblastoma without RB1 mutation [31].

In 80% of cases, this disease is diagnosed before the age of 3-5 years. In high-income countries, patient survival is over 95%, while in low-income countries it is 30%. New international prospective multicentre studies and the search for blood biomarkers that can predict the risk of micrometastasis may contribute to better patient stratification. Currently, the genetic diagnosis of RB requires classical chromosomal studies, MLPA (multiplex ligation-dependent probe amplification) - dependent amplification analysis and Sanger sequencing, fast next generation sequencing (NGS) and RB1 custom array-comparative genomic hybridization (aCGH). However, these methods have some limitations. Molecular genetic studies of RB make a significant contribution to improving the effectiveness of medical genetic counseling, affecting all the components of this process: clarifying the etiology, concretizing the prognosis of offspring and health are relevant for prenatal diagnosis and prevention.

Prenatal screening. Children with a family history of retinoblastoma who carry the RB1 mutation are at risk of tumors at birth. A chorionic villous test is performed to detect malformations and / or genetic diseases in the fetus. A chorionic villous test is taken at 10-13 weeks of gestation or amniocentesis (after 16 weeks of gestation) so that parents have a choice how to manage the pregnancy if the fetus has an RB1 mutation. Amniocentesis may also be offered at 33 weeks' gestation when the risk of miscarriage is lower and manageable [5].

Epigenetic biomarkers in retinoblastoma. In addition to genetic mechanisms, epigenetic mechanisms play an important role in the progression of RB. It has been demonstrated that various epigenetic changes can act as potential biomarkers of the pathogenesis of RB. Studies have shown that Rb1 is involved in the regulation of most major epigenetic changes, including site-specific DNA methylation, histone modification, microRNA (miRNA) and long non-coding RNA (lncRNA) modification, and ATP-dependent chromatin remodeling [32,33]. It has been shown that RB1 inactivation can lead to dysregulation of the tumor suppressor and oncogenic pathways through epigenetic mechanisms [18]. Moreover, the reprogramming of epigenomics is essential for oncogenesis and provides a relatively new avenue for therapeutic targets against RB, since epigenetic modifications can be reversible [34,35]. Thus, epigenetic regulators should be integrated into approaches defining new RB therapies.

Biomarkers from proteomic analysis in retinoblastoma. Proteomics is a systematic study to study the expression of common proteins in cells and tissues, and proteomics analysis is an accurate, high-throughput protein identification strategy [36,37]. In recent years, the advent of proteomics technology has provided a solid foundation for a better understanding of the pathogenesis of RB through the global discovery and quantification of proteins. These high-throughput gel-free proteomics technologies such as iTRAQ, ESI-MS/MS and LC-MS/MS combined with bioinformatic analysis can identify thousands of proteins for proteomic profiling in RB. iTRAQ (isobaric tags for relative and absolute quantitation) is a method for labeling amines in peptides, the peptides are then fractionated with bRPLC. The use of ESI-MS/MS and LC-MS/MS can then be used to identify and quantify the protein[38]. Finally, the identified proteins are subjected to bioinformatic analysis and annotation. Overall, these strategies can reveal a complex proteomic signature as well as potential biomarkers in RB.

Radiogenomic biomarkers in retinoblastoma. Radiogenomics, also referred to as imaging genomics, is a rapidly evolving term that can be used to reveal the relationship between genetic variation and imaging features. The term radiogenomics was introduced by Andreassen et al. in 2002 [39]. Over the past 20 years, genomic data such as DNA, RNA and DNA-seq microarrays have gradually emerged. This allows radiogenomics to be used not only as vital imaging for disease diagnosis, but also to establish new correlations with cellular genomics. Based on these studies, many researchers have used this to identify imaging biomarkers for diagnosis, especially for non-invasive genotyping. Given the promising results, these imaging features could be a replacement for conventional genomics. In the study of Jeasen et al [40], they explored two different ways to identify MR imaging features as biomarkers for utilitarian gene pathways and RB progress. One of the two ways was the assessment of the predefined photoreceptor- related gene expression signature, called photoreceptorness. As we have described above, pRB protein depletion induced RB cells to differentiate from cone precursors. RB without photoreceptorness became poorly differentiated morphologic characteristics in advanced stages of RB and loss of this photoreceptorness gene expression was related to drug sensitivity in vivo[41-42]. From this study, MR features suggested that this photoreceptorness could act as an indicator for advanced stages of RB. Thus, radiogenomic biomarkers may play a potential role in both predictive prognosis and accurate patient management. Based on the foregoing, retinoblastoma is a rare type of cancer and its treatment as well as diagnosis is difficult due to mutations in tumor suppressor genes and the lack of targeted, effective and cost-effective therapies, indicating a significant need for new approaches to address these problems.

Another biomarkers in retinoblastoma. Biomarkers from gene single-nucleotide polymorphism of retinoblastoma. Recently, investigations have identified other genetic biomarkers such as gene polymorphism, which can affect disease progression. These genetic biomarkers can not only help us to effectively understand RB pathogen-

esis, but also induce the development of new therapeutic methods. The TP53 gene is well known to be the most frequently mutated gene in human cancer. In addition to mutations, there are > 20 different coding region single nucleotide polymorphisms (SNPs) in the TP53 gene. Several of these SNPs are known to alter p53 pathway function[43]. It has been suggested that the p53 pathway targets pRB for degradation and in physiological conditions controls the cell cycle and apoptosis in retinal cone precursor cells, from which the RB cell lineage originates[44]. The Arg to Pro change in codon 72 (also known as p.Arg-72Pro, rs1042522 G>C) is the most frequently studied functional SNP in p53. Previous studies have shown that p53 rs1042522 modulates susceptibility to hereditary RB in an Italian population[45]. However, no association was found between RB cancer risk and the rs1042522 genotype in a Chinese population. Interesting, the heterozygous genotype of p53 rs1042522 is significantly associated with decreased RB invasion in a Chinese Han population. Furthermore, subgroup analyses supported the association between the p53 rs1042522 GC genotype and RB invasion among patients with a lag time greater than 1mo or without pre-enucleation treatment. Therefore, these findings may be useful in the near future for the promotion of prevention strategies guided by the patient's genotype because the p53 rs1042522 genotype and clinical characteristics (lag time and pre-enucleation treatment) were associated with a reduced risk of RB invasion[46].The MDM2 gene is an important negative regulator of the p53 suppressor gene, promoting the degradation of p53 through its E3 ubiquitin ligase activity[47]. The polymorphism in MDM2 most widely studied is rs2279744 (also known as MDM2 SNP T309G), which is a T>G transversion SNP on human chromosome 12. An increased risk of RB was found for the MDM2 rs2279744 polymorphism. Also, this SNP could increase the affinity of the transcriptional activator Sp1 which increases the expression of MDM2 DNA and protein, ultimately leading to the attenuation of the p53 pathway. These results determined that the MDM2 rs2279744 polymorphism may be a risk factor for the development of RB. Likewise, it has also been shown that the MDM2 rs937283 polymorphism was significantly associated with decreased risk of RB. The MDM2 rs937283 SNP, known as G2164A, leads to an A to G base change at the nucleotide 2164 in the promoter region of MDM2 gene[48]. The MDM4 gene (also known as MDMX), located on chromosome 1q32, is described as an MDM2 homologue with high structural similarity which has been shown to promote the proteasome-mediated degradation of p53 and negatively regulate the p53 pathway. It was observed that MDM4 is overexpressed in RB compared with fetal retina[49]. Recent studies have reported that both the AA genotype and the A allele at MDM4 rs11801299 were related to an increased risk of developing RB as well as tumor invasion and poor pathological differentiation. Further, the G allele at rs1380576 reduced the risk of developing RB, and was associated with low tumor aggressiveness. In addition, the G allele at rs11801299 reflected poor prognosis of RB patients[50].Another meaningful SNP is rs4938723 T>C, which is located in the promoter region in the mir-34b/c gene and alters mir-34b/c gene expression. The mir-34b/c inhibits p53 antagonists and pro-apoptotic proteins and it is a part of the p53 pathway. A recent study has implied that a germline Rb1 mutation and the SNP rs4938723CC of the mir-34b/c gene can speed RB genesis and patients with these mutations could have earlier diagnosis. Thus, the mir-34b/c SNP rs4938723 T>C may act as a potential biomarker for hereditary RB. Though the interaction of SNPs can provide novel markers for RB prognosis, diagnosis, and treatment, further studies need to be done.Besides biomarkers for RB diagnosis, prognosis, and therapy, genetic biomarkers to define high-risk RB are also essential to reduce mortality. Nowadays, the calculation of RB clinical risk is mainly determined by histopathologic features combined with clinical traits. These features, called high-risk histopathologic features (HRFF), are detected in most RB cases[51]. However, there is a small portion of RB patients that do not have these typical features even after progressing to metastasis and death[52]. Thus, it is important to discover additional biomarkers to predict high risk RB and the effect of chemotherapy. Cellular anaplasia, which is different from cellular differentiation, indicated high-risk RB and predicted the RB metastases even without HRRFs. Furthermore, as we all know, gene profiles could assist researchers in identifying mechanisms devoted to anaplastic severity and define genetic markers of anaplastic grades. Hudson et al[53] conducted gene profiles to characterize anaplastic grades in RB, and showed that different anaplastic grades have various gene expressions. Especially in severe anaplasia, photoreceptor and nucleoporin expression were highly dysregulated, including downregulation of photoreceptor genes and markedly increased nucleoporin expression. A limited gene set consisting of EXOC8, CHTOP, NUCKS1, and ADSS accurately separated severe anaplasia from all other samples, which means this gene set could predict severe anaplasia. Overall, these results contribute to identification of biomarkers for high-risk RB.

Conclusions. Molecular genetic study of structural damage to the RB1 gene in retinoblastma is necessary to confirm or exclude the hereditary nature of the disease, which will allow choosing a timely and adequate algorithm for monitoring and treating the tumor, as well as planning further childbearing. The inclusion of modern methods of molecular genetic analysis in a comprehensive examination of patients allows expanding the possibilities of early diagnosis, the use of organ-preserving methods in its treatment and prevention, which allows saving not only life, but also the eyeball and vision in a child.

Thus, the analysis of the literature suggests that these biomarkers require further study and can not only play a decisive role in the biological processes of RB, but also help to compare and confirm the diagnosis, determine therapeutic targets, or serve as a prognostic indicator of treatment.

REFERENCES

1 Dimaras H., Corson T.W., Cobrinik D. et al. Retinoblastoma // Nat Rev Dis Primers.- 2015.-№1, Vol.15.- p.21.
2 Kivelä T. The epidemiological challenge of the most frequent eyecancer: retinoblastoma, an issue of birth and death. // Br J Ophthalmol.2009.№93(9). -p.1129-1131.
3 Vijitha S., Vempuluru., Swathi Kaliki. Screening for Retinoblastoma: A Systematic Review of Current Strategies. //Asia Pac J Ophthalmol (Phila) .-2021.№10.-p.192–199.
4 Mayra Mart´ınez-Sa´nchez, Jesu´s Hernandez-Monge, Martha Rangel et al. Retinoblastoma: from discovery to clinical management // The FEBS Journal.-2022.-№289.-P.4371–4382.
5 Soliman S.E., Racher H., Zhang C. et al. // Genetics and molecular diagnostics in retinoblastoma--an update // Asia Pac J Ophthalmol (Phila). -2017.-№6.-P.197–207.
6 Benavente C.A., Dyer M.A. Genetics and epigenetics of human retinoblastoma // Annu Rev Pathol.-2015.-№10.-p.547.
7 Chunsik lee, Jong Kyong Kim. Genome maintenance in retinoblastoma: Implications for therapeutic vulnerabilities (Review) //Oncology Letters.-2022.-№23.-p.192.
8 Knudson A.G. Two genetic hits (more or less) to cancer // Nat Rev Cancer. -2001.-№1.- P157–162.
9 Mendoza P.R., Grossniklaus H.E. The biology of retinoblastoma // Prog Mol Biol Transl Sci. -2015.-№134.-P.503–516.
10 Lande K., Gupta J., Ranjan R., Kiran M., Torres Solis L.F., Solís Herrera A., Aliev G., Karnati R. et al. Exosomes: Insights from Retinoblastoma and Other Eye Cancers // Int J Mol Sci. -2020.-№21, Vol,19. – p.7055.
11 Temming P., Arendt M., Viehmann A. et al. Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: a report from the German reference center // Pediatrician Blood Cancer. -2017.- №64.-P.71–80.
12 Friedman D.N., Sklar C.A., Oeffinger K.C. et al. Long-term medical outcomes in survivors of extra-ocular retinoblastoma: the Memorial Sloan-Kettering Cancer Center (MSKCC) experience // Pediatrician Blood Cancer.- 2013.- №60.-P.694–699.
13 Avetisov E.S., Kovalevsky E.I., Khvatova A.V. Handbook of pediatric ophthalmology.// Moscow: Meditsina, 1987, p.440.
14 Balmer A, Munier F. Differential diagnosis of leukocoria and strabismus, first presenting signs of retinoblastoma. //Clin Ophthalmol. -2007,№1,-p.431–439.
15 Tonorezos E.S., Friedman D.N., Barnea D., Bosscha M.I., Chantada G., Dommering CJ, de Graaf P. // Ophthalmology. -2020.- №127, Vol.11.-P.1549-1557.
16 Mendoza P.R., Specht C.S., Hubbard G.B., Wells J.R., Lynn M.J., Zhang Q., Kong J., Grossniklaus H.E. Histopathologic grading of anaplasia in retinoblastoma. //Am J Ophthalmol.- 2015.- №.159, Vol 4. – P.764-776.
17 Sampieri, K., Amenduni, M., Papa, F.T., Katzaki, E., Mencarelli, M.A., Marozza, A., Epistolato, M.C., Toti, P., Lazzi, S., Bruttini, M., et al. Array comparative genomic hybridization in retinoma and retinoblastoma tissues. //Cancer Sci.- 2009, №100, -p.465–471.
18 Munier, F.L., Beck-Popovic, M., Chantada, G.L., Cobrinik, D., Kivela, T.T., Lohmann, D., Maeder, P., Moll, A.C., Carcaboso, A.M., Moulin, A., et al. Conservative management of retinoblastoma: Challenging orthodoxy without compromising the state of metastatic grace. “Alive, with good vision and no comorbidity”. //Prog. Retin. Eye Res. -2019,№73.P.100764.
19 Chen, D.N., Gallie, B.L., Squire, J.A. //Minimal regions of chromosomal imbalance in retinoblastoma detected by comparative genomic hybridization. Cancer Genet. Cytogenet. -2001, №129, -p.57–63.
20 Hudson, L.E.. Mendoza, P., Hudson, W.H., Ziesel, A., Hubbard, G.B., 3rd, Wells, J., Dwivedi, B., Kowalski, J., Seby, S., Patel, V. et al.Distinct gene expression profiles define anaplastic grade in retinoblastoma. // Am. J. Pathol. -2018, №188,- p.2328–2338.
21 Lillington, D.M., Kingston, J.E., Coen, P.G., Price, E., Hungerford, J., Domizio, P., Young, B.D., Onadim, Z. Comparative genomic hybridization of 49 primary retinoblastoma tumors identifies chromosomal regions associated with histopathology, progression, and patient outcome. // Genes Chromosomes Cancer -2003, №36, p.121–128.
22 Mairal, A., Pinglier, E., Gilbert, E., Peter, M., Validire, P., Desjardins, L., Doz, F., Aurias, A., Couturier, J. Detection of chromosome imbalances in retinoblastoma by parallel karyotype and CGH analyses. // Gene Chromosome Cancer.- 2000,№ 28, p.370–379.
23 Mol, B.M., Massink, M.P., van der Hout, A.H., Dommering, C.J., Zaman, J.M., Bosscha, M.I., Kors, W.A., Meijers-Heijboer, H.E., Kaspers, G.J., Riele, H., et al. High resolution SNP array profiling identifies variability in retinoblastoma genome stability. //Genes Chromosomes Cancer.- 2014, №53,-p.1–14.
24 Zielinski, B., Gratias, S., Toedt, G., Mendrzyk, F., Stange, D.E., Radlwimmer, B., Lohmann, D.R., Lichter, P. Detection of chromosomal imbalances in retinoblastoma by matrix-based comparative genomic hybridization. //Genes Chromosomes Cancer. -2005, №43, p.294–301.
25 Berry, J.L., Lewis, L., Zolfaghari, E., Green, S., Le, B.H.A., Lee, T.C.. Lack of correlation between age at diagnosis and RB1 mutations for unilateral retinoblastoma: The importance of genetic testing. Ophthalmic Genet. -2018.№39.P. 407–409.
26 Cui, Z., Guo, Y., Zhou, Y., Mao, S., Yan, X., Zeng, Y., Ding, C., Chan, H.f., Tang, S., Tang, L., et al. Transcriptomic analysis of the developmental similarities and differences between the native retina and retinal organoids. Investig. //Ophthalmol. Vis. Sci. 2020, 61, 6.
27 Afshar, A.R., Pekmezci, M., Bloomer, M.M., Cadenas, N.J., Stevers, M., Banerjee, A., Roy, R., Olshen, A.B., Van Ziffle, J., Onodera, C., et al. Next-generation sequencing of retinoblastoma identifies pathogenic alterations beyond RB1 inactivation that correlate with aggressive histopathologic features. // Ophthalmology 2019.
28 Marchong, M.N., Chen, D., Corson, T.W., Lee, C., Harmandayan, M., Bowles, E., Chen, N., Gallie, B.L. Minimal 16q genomic loss implicates cadherin-11 in retinoblastoma. //Mol. Cancer Res. -2004, №2, p.495–503.
29 Ewens, K.G., Bhatti, T.R., Moran, K.A., Richards-Yutz, J., Shields, C.L., Eagle, R.C., Ganguly, A. Phosphorylation of pRb: Mechanism for RB pathway inactivation in MYCN-amplified retinoblastoma. // Cancer Med.- 2017, №6, p.619–630.
30 Harini V. Gudiseva., Jesse L. Berry, Ashley Polski., Santa J. Tummina. Next-Generation Technologies and Strategies for the Management of Retinoblastoma. Genes.- 2019.№10.-P. 1032, doi:10.3390/genes10121032
31 Rushlow, D.E., Mol, B.M., Kennett, J.Y., Yee, S., Pajovic, S., Theriault, B.L., Prigoda-Lee, N.L., Spencer, C., Dimaras, H., Corson, T.W., et al. //Characterisation of retinoblastomas without RB1 mutations: Genomic, gene expression, and clinical studies. //Lancet Oncol. 2013, №14,p.327–334.
32 Wilting R.H., Dannenberg J.H. Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance. //Drug Resist Update.- 2012.- №15.-P.21-38.
33 Sun J., Xi H.Y., Shao Q., Liu Q.H. Biomarkers in retinoblastoma // Int J Ophthalmol.- 2020.- №13, Vol.2. – P.325-341.
34 Zhang J., Benavente C.A., McEvoy J., et al. A novel retinoblastoma therapy from genomic and epigenetic analyses // Nature.- 2012.- №481, Vol.7381. – P. 329-334.
35 Patel D.J., Wang Z. Readout of epigenetic modifications // Annu Rev Biochem. – 2013.- №82.-P.81-118.
36 Rabia Arshad, Mahmood Barani, Abbas Rahdar. Multi-Functionalized Nanomaterials and Nanoparticles for Diagnosis and Treatment of Retinoblastoma // Biosensors.- 2021.- №11, Vol.4.-p. 97.
37 Mallikarjuna K., Sundaram C.S., Sharma Y., Deepa P.R., Khetan V., Gopal L., Biswas J., Sharma T., Krishnakumar S. Comparative proteomic analysis of differentially expressed proteins in primary retinoblastoma tumors // Proteomics Clin Appl. – 2010. -№4,Vol.4.-P.449-463.
38 Rossukon Kaewkhaw, Duangnate Rojanaporn. Retinoblastoma: Etiology, Modeling, and Treatment // Cancers.- 2020.- №12.-P. 2304-2323.
39 Himika Gupta, Sivasankar Malaichamy3, Ashwin Mallipatna, et al. Retinoblastoma genetics screening and clinical management // BMC Med Genomics.-2021.- №14. – p.188.
40 Jansen R.W., de Jong M.C., Kooi I.E., Sirin S, Göricke S,. MR imaging features of retinoblastoma: association with gene expression profiles. // Radiology.-2018, № 288(2),-p:506-515.
41 Kooi I.E., Mol B.M., Moll A.C., van der Valk P., de Jong M.C., de Graaf P., van Mil S.E., Schouten-van Meeteren A.Y., Meijers-Heijboer H., Kaspers G.L., Te Riele H., Cloos J., Dorsman J.C. Loss of photoreceptorness and gain of genomic alterations in retinoblastoma reveal tumor progression. // EBioMedicine. -2015, №2(7):P.660-670.

42 Kapatai G., Brundler M.A., Jenkinson H., Kearns P, Parulekar M, Peet A.C., McConville C.M., Gene expression profiling identifies different sub-types of retinoblastoma. // Br J Cancer.- 2013.- №109(2):P.512-525.
43 Barnoud T, Parris JLD, Murphy ME. Common genetic variants in the TP53 pathway and their impact on cancer. J Mol Cell Biol. 2019;11(7):578–585.
44 Xu XL, Fang Y, Lee TC, Forrest D, Gregory-Evans C, Almeida D, Liu A, Jhanwar SC, Abramson DH, Cobrinik D. Retinoblastoma has properties of a cone precursor tumor and depends upon cone-specific MDM2 signaling. Cell. 2009;137(6):1018–1031.
45 Epistolato MC, Disciglio V, Livide G, Berchialla P, Mencarelli MA, Marozza A, Amenduni M, Hadjistilianou T, De Francesco S, Acquaviva A, Toti P, Cetta F, Ariani F, De Marchi M, Renieri A, Giachino D. p53 Arg72Pro and MDM2 309 SNPs in hereditary retinoblastoma. J Hum Genet. 2011;56(9):685–686.
46 Chen R, Liu S, Ye H, Li J, Du Y, Chen L, Liu X, Ding Y, Li Q, Mao Y, Ai S, Zhang P, Ma W, Yang H. Association of p53 rs1042522, MDM2 rs2279744, and p21 rs1801270 polymorphisms with retinoblastoma risk and invasion in a Chinese population. Sci Rep. 2015;5:13300.
47 Bond GL, Hu W, Bond EE, Robins H, Lutzker SG, Arva NC, Bargonetti J, Bartel F, Taubert H, Wuerl P, Onel K, Yip L, Hwang SJ, Strong LC, Lozano G, Levine AJ. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell. 2004;119(5):591–602.
48 Cao Q, Wang Y, Song X, Yang W. Association between MDM2 rs2279744, MDM2 rs937283, and p21 rs1801270 polymorphisms and retinoblastoma susceptibility. Medicine (Baltimore) 2018;97(49):e13547.
49 Laurie NA, Donovan SL, Shih CS, Zhang J, Mills N, Fuller C, Teunisse A, Lam S, Ramos Y, Mohan A, Johnson D, Wilson M, Rodriguez-Galindo C, Quarto M, Francoz S, Mendrysa SM, Guy RK, Marine JC, Jochemsen AG, Dyer MA. Inactivation of the p53 pathway in retinoblastoma. Nature. 2006;444(7115):61–66.
50 Yu F, Jiang Z, Song A. Association of rs11801299 and rs1380576 polymorphisms at MDM4 with risk, clinicopathological features and prognosis in patients with retinoblastoma. Cancer Epidemiol. 2019;58:153–159.
51 Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. Cancer. 1994;73(3):692–698.
52 Mabtum ED, Bonanomi MT, Lima PP, Almeida MT. Orbital retinoblastoma: case report. Arq Bras Oftalmol. 2013;76(4):247–249.
53 Hudson LE, Mendoza P, Hudson WH, Ziesel A, Hubbard GB, 3rd, Wells J, Dwivedi B, Kowalski J, Seby S, Patel V, Geisert E, Specht C, Grossniklaus HE. Distinct gene expression profiles define anaplastic grade in retinoblastoma. Am J Pathol. 2018;188(10):2328–2338

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