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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Association of *BAP1* polymorphisms with development of uveal melanoma

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Abstract. *Relevance.* Uveal melanoma is a rare form of cancer that originates in the eye, most frequently arises in the choroid (90%). *BAP1* is a tumor suppressor gene, mutations in this gene were found in 40–84% of primary UM. Given many investigators have proven the association of mutations in the *BAP1* gene with UM. *Aim*: our study aims to figure out UM associated polymorphisms by sequencing DNA in exon 10, exon 11, exon 15, exon 16, and exon 17 as well as to assess the role of *BRCA1* mutations in risk of UM development. *Materials and Methods*. A total of 95 individuals recruited in the study, out of them 42 as a patient group, 23 as a risk group, and 30 as a control group. The target regions of *BAP1* gene amplified by PCR were sequenced by Sanger method and *BRCA1* was genotyped by real-time PCR using commercially produced kits. *Results and Discussion*. This study did not demonstrate presence of any polymorphisms in the sequenced regions of the *BAP1* gene or the genotyped specific *BRCA1* sites that are correlated with an increased risk of uveal melanoma development. Our findings do not deny the published strong association between *BAP1* inactivating mutations and the UM disease. This study's findings instead propose that within this targeted population, the molecular mechanisms for BAP1 loss-function may include aberrations other than changes in the examined exons. *Conclusion*. Consequently, we recommend future research that includes sequencing the entire *BAP1* gene in larger sized samples and studying of other candidate genes.

Keywords: uveal melanoma, BAP1, BRCA1

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Author contributions. Mukhana L. performed genotyping of study participants and contributed to prepare the manuscript. Ahmed A.A.M. analyzed the results and prepared the manuscript. Gigani O.O. contributed to prepare the manuscript, Saakyan S.V. clinically examined and selected the patients recruited in the study. Tsygankov A. Yu. clinically examined patients recruited in the study and collected the biological material. Azova M.M. designed the study. All authors made significant contributions to the conception, conduct of the study and preparation of the article, read and approved the final version before publication.

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Introduction

Uveal melanoma (UM) is a rare and serious form of cancer that arises from melanocytes of the uvea. Uvea is the middle tissue layer in the wall of the eye, which compresses the iris, ciliary body, and choroid. It is molecularly distinct from cutaneous melanoma, primarily due to a different pattern of driver mutations. This subtype of melanoma is the most common primary intraocular cancer in adults. Roughly 50% of all UM patients will develop metastasis to other sites, including the liver (most common site), the lungs, and bones. The mean incidence rate of uveal melanoma is approximately 5.0 cases per million people per year. Males have a higher incidence rate of 5.9 per million in comparison to females with an average incidence rate of 4.5 per million [1]. Understanding UM aetiology carries unique challenges in comparison to cutaneous melanoma, which remains an area of active research. The aetiology of uveal melanoma is influenced by many factors that contribute to its development. Both genetic and environmental factors are included in UM aetiology, or can emerge from a complex interplay of genetic and environmental factors [2–6]. Genetic contribution occurs in approximately 80% of UM cases. A comprehensive investigation of UM genomes has revealed a total of 130 genetic mutations. Somatic and germline mutations in some genes; *BAP1*, *GNAQ*, *GNA11*, *SF3B1*, *SRSF2*, *EIF1AX*, *PLCB4*, *CYSLTR2*, and *TERT*, are being notably recurrent UM and thought to play a critical role in tumor initiation and progression [2, 3, 4]. Mutations in the TP53 gene are a common cause of p53 disruption in many cancers [7], but they occur only rarely in uveal melanoma (UM), despite p53's frequent involvement in cancer overall [8]. Additionally, chromosomal alterations are also significant in UM, where have been found a loss of chromosome 3, its short arm or other chromosomal regions, has been associated with a higher risk of metastasizing UM [9, 10].

BAP1 refers to the BRCA1 associated protein-1 gene located on chromosome 3 in the region p21.31-p21.2. The gene codes for an enzyme that consists of 729 amino acids. BAP1 is a nuclear-localized protein that belongs to the subfamily of deubiquitinase enzymes. It contains a ubiquitin C-terminal hydrolase (UCH) domain that gives it deubiquitinating activity involved in removal of ubiquitin molecules from target proteins. By removing ubiquitin tags, BAP1 can stabilize targeted proteins and prevent their degradation by the proteasome. Accordingly, BAP1 orchestrates the stability and function of several proteins involved in cell cycle control, DNA repair, transcription, tumor suppression, and chromatin dynamics. Loss of BAP1 function can lead to genome instability and contribute to the development of various malignancies [11,12].

It has been found, *BAP1* is deleted or mutated in diverse human cancers and its re-expression reversed their tumorigenicity. This is suggesting that BAP1 might function as a tumor suppressor protein that prevents uncontrolled cell growth and division [11]. Therefore, the enzyme probably exerts its function by tightly regulating various cellular processes through deubiquitination of its substrates. The processes regulated by BAP1 include; regulation of cell cycle, transcription growth, and cellular differentiation. It also responds to DNA damage and chromatin dynamics.

Three functional domains constitute BAP1 protein, two binding domains and one catalytic domain. The binding and catalytic domain (UCH) (approximately amino acid residues 1–240) located at the N-terminal, is responsible for binding to host cell factor-1 (HCF-1) and functions as ubiquitin carboxy-terminal hydrolase. The second domain (amino acid residues 182–365 encoded by multiple exons including exon 10) is a binding region also located at the N-terminal interacting with BARD1 and UCH37-Like domain (ULD), reported that a mutation in this region is associated with development of cancer [13]. The third one is also a binding domain (approximately amino acid residues 675–693 encoded by exons 15,16,17) located at the C-terminal interacting with BRCA1 and ASXL [14–16]. The BAP1 enzyme enhances the BRCA1 tumor suppressor activity through interaction with the RING finger domain of BRCA1 and BARD1 proteins and acts as a tumor suppressor [11, 17]. BAP1 interacts with BARD1 to inactivate the E3 ligase activity of BRCA1/BARD1. The E3 ligase is responsible for the addition of ubiquitin to specific proteins to regulate DNA repair, cell cycle, and chromatin remodeling [17].

BAP1 with high affinity interacts directly with ASXL1, ASXL2, and ASXL3 through the ASXH domain. The BAP1 binding to ASXL proteins is to form the active PR-DUB complex crucial for its proper function of tumor suppression. The interaction of BAP1 with the DEUBAD domain of ASXL proteins through the C-terminal ULD is mandatory for stimulating its activity. Consequently, ASXL binding is significantly enhancing BAP1 ability to deubiquitinate its main substrate, histone H2A at lysine 119 in humans [18]. It has been found that BAP1 promotes the ubiquitination of ASXL2 to stabilize it, in turn which stimulates its own deubiquitinase activity [19]. The deubiquitin hydrolase activity of BAP1 is strongly stimulated by the direct binding of the ASXL2 AB box to the BAP1-ULD domain. This interaction is obligatory for BAP1 enzymatic activity and that many *BAP1* mutations allosterically inhibit BAP1-ASXL2 binding [16].

The alteration in this gene takes a significant part in various cancers, including uveal melanoma. As well as *BAP1* mutations are identified at low prevalence in many cancer diseases including mesothelioma, bladder, breast, pancreatic, and colorectal cancers [11]. Several studies have reported that mutations in *BAP1* gene are strongly associated with poor prognosis and increased risk of metastasis in UM patients [2–4, 12]. Somatic *BAP1* mutations were recognized in roughly 84% of UM patients. Germline *BAP1* mutations were found in approximately 8% of metastatic tumors originated from metastasizing uveal melanoma [10,11,20]. According to statistical findings of published studies, human carriers of inherited inactivated *BAP1* gene are strongly at a high risk of developing at least one and often many cancers, in particular UM, during their lifetime. This guided to infer that inherited *BAP1*-inactivating mutations have a penetrance approaching 100% [11, 21].

In the context of significant predisposition of aberrant *BAP1* carriers to cancers in particular uveal melanoma, the ongoing study aims to detect new polymorphisms in the exome of *BAP1* gene. Thereby, our study focused on analysis of the sequence of coding regions including the exons 10, 11, 15, 16, and 17 in the candidate *BAP1* gene. The analysis of these regions may help recognize any pathogenic or likely pathogenic variants might be associated with a risk of developing uveal melanoma among Russians. Giving that ASXL is essential for the BAP1 ubiqutination activity, we have targeted these exons to sequence since they encode the BAP1 domains that bind to ASXL, BCRA1, and BARD1 proteins [13], this interaction is verry essential for the tumor suppression function of BAP1. Our expectation was that presence of polymorphisms at these exons can fail the interaction of BAP1 and ASXL and inhibits BAP1 activity. Additionally, since BRCA1 functions together with the BAP1 to

suppress tumor development, we genotyped the following *BRCA1* polymorphisms; 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA). The *BRCA1* genotyping aimed to assess whether the chosen mutations play roles in uveal melanoma formation. Recognition of pathogenic or likely pathogenic variants associated with a higher risk of developing uveal melanoma among Russians may provide novel insights into predictive biomarkers for diagnosis and managing hereditary UM risks within families.

Materials and methods

Participants and samples

The participants were classified into three groups: the case group consisted of 42 patients suffering from UM and choroidal nevus, with the mean age of 56.3 ± 9.8 years, the risk group composed of 23 patients with benign choroidal nevus, with the mean age of 47.5 ± 7.9 years, and the control group included 30 healthy volunteers with no history of intraocular neoplasms, with the mean age of 39.63 ± 12.07 years. The DNA sequences from the UM patients, individuals at risk of UM, and healthy individuals were compared to a reference DNA sequence in NCBI database to identify any nucleotide base pair abnormalities. The sequencing analysis targeted the exon 10, exon 11, exon 15, exon 16, and 17 as well as the introns between the exons 15–17 performed for the genomic DNA extracted from all the samples of studied groups. Genotyping for *BRCA1* polymorphisms was performed by real-time PCR.

DNA extraction, PCR and sequencing and genotyping of SNPs

Genomic DNA was isolated from leucocytes of peripheral blood samples of all the study participants by standard procedures using a commercially available kit (EX-509–100 DNA-extran-1 kit; Syntol, Russia). Extracted DNA was kept at –20 °C. DNA sequencing was performed using the Sanger method in Syntol Laboratory. Sequencing of *BAP1* included the coding regions of the 10th and 11th, 15th, 16th, 17th exons as well as the introns between 15th, 16th, and 17th exons. The PCR products were separated by gel electrophoresis on a 2% agarose gel, visualized by ethidium bromide under UV light, and then prepared for sequencing with a purification kit (Cleanup S-cap, Evrogen, Russia) following the manufacturer's protocol. The target regions were amplified using PCR according to the following thermocycling conditions. For exon 10 and exon 11: initial denaturation at 95 °C for 5 minutes and 40 cycles of amplification at 95 °C for 30 seconds, annealing at 60 °C (exon 11) or 65 °C (exon 10) for 30 seconds, extension at 72 °C for 30 seconds, and a final extension step at 72 °C for 5 minutes. For exon 15, exon 16, and exon 17: initial denaturation at 95 °C for 10 minutes and 40 cycles of amplification at 95 °C for 45 seconds, annealing at 58 °C for 40 seconds, extension at 72 °C for 60 seconds, and a final extension step at 72 °C for 10 minutes. The primers used for PCR amplification were designed using Primer-BLAST as presented in the table.

Primers, annealing temperature, and amplified fragment size for the analyzed exons of *BAP1* gene

Exons of *BAP1*gene	Primers	Length of PCR product	Annealing temperature
Exon10	F:5'-AGAGAATCCTGCAAGGGTGC-3' R:5'-CCCTGTCTCAGATGGTGCAG-3'	175bp	65 °C
Exon 11	F:5'-CCCCAGTACCTGTGTGGTT-3' R:5'-CCTGGATTCTGTTGTTAGCTGAT-3'	225bp	60 °C
Exons 15, 16, 17	F: 5'-AGGGGCCTTGATAGGCATGG-3' R:5'-TAATACTGGGAAAAGGGGAAGTGG-3'	789bp	58 °C

Genotyping for the *BRCA1* 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA) was performed by PCR using RealBEST-Genetics reagent kits from VectorBEST (Russia) according to the manufacturer's protocol.

Results and discussion

Our sequencing results for all the analyzed exons as well as the last two introns (between exons 15–16 and exons 16–17) have not revealed any polymorphisms relevant to the risk of uveal melanoma development. The DNA sequencing in our study did not detect any changes in the *BAP1* nucleotide sequence between the healthy volunteers and uveal melanoma patients in Russian population. To the best of knowledge, different studies indicate that mutations in *BAP1* frequently found in uveal melanomas are monosomy 3 (chromosome 3 loss) and large deletions including the *BAP1* locus itself [22]. Our study as well as results of other researchers necessitate a further investigation of whole *BAP1* gene sequencing, copy number variation assessment, and analysis of promoter or deep intronic regions in a larger sized-sample of people to fully elucidate the role of *BAP1* in uveal melanoma. Our findings coincide with the results of many investigators overall the world, so here we are shedding light on their explanations and conclusions about correlation of *BAP1* mutations with uveal melanoma. Truncating mutations (nonsense, frameshift) lead to a complete loss of BAP1 function, severely impairing both homologous recombination and nucleotide excision repair pathways. As a result, cells exhibit increased sensitivity to DNA-damaging agents and a higher accumulation of genetic defects, contributing to cancer progression [23]. While these mutations may alter BAP1 function, they often do not completely abolish its activity. The impact of missense mutations on DNA repair can vary, but they are generally associated with less severe consequences than truncating mutations [23].

Pathogenic *BAP1* mutations are predominantly found in the ubiquitin C-terminal hydrolase domain of the BAP1 protein, which is essential for its deubiquitinating activity. This suggests that the loss of this function plays a crucial role in UM progression and the metastatic process. Other mutations occur in binding domains for BARD1, BRCA1, ASXL, and HCF-1 proteins, which may impair their functional stability so that affecting cellular functions related to tumor suppression.

The absence of *BAP1* nucleotide sequence changes in our study contrasts with the well-established role of BAP1 inactivation, often through large deletions on chromosome 3. It is possible that the changes were in the non-analyzed regions of the gene targeted by our study or the predisposition to UM is caused by polymorphisms of other genes. On this point of view, our findings and those of other literatures could extract that the fundamental mechanism of BAP1 inactivation in UM is mostly not due to point mutations in the coding sequence but rather due to large-scale deletions that comprise the entire BAP1 locus. As well as it could arise due to mutations in regions that silence the gene transcription, such as promoter, deep intronic regions, which could hinder mRNA splicing and the other exons not covered by our study or other previous sequencing studies.

There were no significant changes between the experimental group, the risk group, and the control group when the frequency of different alleles of loci 4153delA, 5382insC, 185delG, 3875del14, T300G, 2080delA (insA) of *BRCA1* was examined. In every group, the normal allele was found in 100% of cases, except for the *BRCA1 4153delA*. All patients in the risk group were homozygous for the normal allele, except for one patient (4.34%) who was heterozygous for the *BRCA1 4153delA* mutation. Our findings coincide with the published findings that failed to reveal a significant association between *BRCA1* mutations and uveal melanoma.

Additionally, as indicated in a previously published study, our results detected that uveal melanoma development has a strong association with *BARD1* gene inactivation mutation [24]. This indirectly supports our hypothesis in currently study that uveal melanoma may correlate with damages in different components of nucleotide excision repair pathways.

Conclusion

In summary, our sequencing analysis of the examined exons of the *BAP1* gene and genotyping of specific sites in the *BRCA1* gene within the Russian population did not recognize polymorphisms associated with an increased predisposition to development of uveal melanoma. Consequently, our results do not disprove the strong association between aberrant BAP1 (loss-of-function) and uveal melanoma development demonstrated by published studies. Instead, they postulate that in the Russian population, the mechanisms of *BAP1* inactivation may differ from simple point mutations in the sequenced exons. This leads us to recommend sequencing the whole gene in a larger sample size in different populations and studying for other candidate genes. The complete lack of association with the tested *BRCA1* mutations proves the absence of correlation with UM as reported in previous studies.

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Ассоциация полиморфизмов гена *BAP1* с развитием увеальной меланомы

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Аннотация. *Актуальность*. Увеальная меланома (УМ) представляет собой редкую форму онкопатологии, которая развивается в глазу и наиболее часто возникает в хориоидее (90 %). *BAP1* является геном-супрессором опухолей; мутации в этом гене обнаруживаются в 40–84 % случаев первичной УМ. Учитывая, что многие исследователи показали связь мутаций в гене *BAP1* с УМ. Цель: целью нашей работы стало выявить ассоциированные с УМ полиморфные варианты в экзонах 10, 11, 15, 16 и 17, а также оценить роль мутаций гена *BRCA1* в развитии УМ. *Материалы и методы*. Всего в исследовании приняли участие 95 человек, включая 42 пациента с УМ, 23 пациента из группы риска и 30 добровольцев контрольной группы. Целевые участки гена *BAP1*, амплифицированные с помощью ПЦР, были секвенированы методом Сэнгера; генотипирование по гену *BRCA1* проводилось методом ПЦР в реальном времени. *Результаты и обсуждение*. Настоящее исследование не выявило полиморфных вариантов в секвенированных последовательностях гена *BAP1* и мутаций гена *BRCA1*, которые были бы ассоциированы с повышенным риском развития УМ. Наши результаты не опровергают литературные данные о связи между инактивирующими мутациями *BAP1* и увеальной меланомой, но позволяют предполагать, что молекулярные механизмы потери функции *BAP1* могут включать нарушения за пределами исследованных экзонов. *Выводы*. Таким образом, целесообразны дальнейшие исследования с секвенированием всего гена *BAP1* в выборках большего объёма и изучением других кандидатных генов.

Ключевые слова: увеальная меланома, BAP1, BRCA1

Информация о финансировании. Авторы заявляют об отсутствии финансирования

Вклад авторов. Мухана Л. — генотипирование пациентов, участие в подготовке рукописи; Ахмед А.А.М. — анализ результатов исследования, участие в подготовке рукописи; Гигани О.О. — участие в подготовке рукописи; Саакян С.В. — анализ клинических данных и подбор пациентов; Цыганков А.Ю. — анализ клинических данных и сбор биологического материала; Азова М.М. — дизайн исследования. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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