ОЦЕНКА ВЛИЯНИЯ РЕДКОГО СИНОНИМИЧНОГО ВАРИАНТА ГЕНА *KNG1* НА РАЗВИТИЕ НАСЛЕДСТВЕННОГО АНГИООТЕКА

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Резюме. Основная причина отека при наследственном ангиоотеке (НАО) связана с повышенным уровнем брадикинина, вызванным дефицитом/изменением функциональной активности С1-INH, связанными с мутациями в гене *SERPING1* или мутациями в генах *F12, PLG, ANGPT1, KNG1, MYOF* и *HS3ST6* при нормальном уровне и функциональности ингибитора С1-эстеразы. Выявление новых мутаций, которые могут играть роль в патогенезе НАО, является важным шагом в понимании и лечении заболевания. Однако оценка или анализ влияния конкретных мутаций или комбинаций мутаций на организм остается серьезной проблемой. Целью работы являлся прогностический анализ *in silico* редкого синонимичного варианта NC_000003.12:g.186725098T>C гена *KNG1* и его влияние на развитие симптомов НАО. Материалом служил образец цельной крови, полученный от женщины с клиническими проявлениями наследственного ангиоотека без снижения уровней и функции С1-ингибитора. Методы исследования включали секвенирование полного экзома пациентки, биоинформатический анализ мутации гена *KNG1* с использованием ряда баз данных и веб-ресурсов. Результаты. При обработке данных полноэкзомного секвенирования нами обнаружен синонимичный вариант в гене *KNG1* (экзон 4, изоформа 1): NC_000003.12:g.186725098T>C. Пациентка является гетерозиготным носителем варианта, который, по данным TOPMED, встречается с частотой 0,000004 (1:264690). Однако этот синонимичный вариант не имеет данных о патогенности и не помечен в базе данных ClinVar. Анализ показал, что вариант является патогенным из-за изменений, затрагивающих сайт сплайсинга. Потеря функции возможна в положениях с 28 по 132 (цистатин-кининогеновый домен) и в положениях

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со 120 по 628, среди которых особенно значимы положения 379-380/389-390 (где происходит расщепление калликреина), 380-389 (отвечает за образование Lys-брадикинина) и 381-389 (отвечает за образование брадикинина). Предположительно, выявленный вариант может приводить к развитию спорадических отеков несколькими путями, связанными с образованием брадикинина или его аналогов. А именно: (1) мутантный высокомолекулярный кининоген легче активируется калликреином и становится источником образования брадикинина посредством калликреин-кининовой системы; (2) механизм образования брадикинина претерпевает значительные изменения и приводит к образованию функционально активного, но аберрантного брадикинина, что изменяет его инактивацию ферментами с последующим увеличением периода полужизни; (3) изменения в положениях 380-389 приводят к изменениям в репродукции Lys-брадикинина, так что на последующих этапах он «легче» расщепляется до брадикинина аргининаминопептидазой. Таким образом, результаты нашего исследования указывают на возможную роль идентифицированного варианта гена *KNG1* в развитии НАО. Кроме того, результаты также подчеркивают важность дальнейших исследований синонимичных вариантов гена *KNG1*, которые могут пролить свет на этиологию заболевания.

Ключевые слова: первичные иммунодефициты, наследственный ангиоотек, анализ патогенности мутации, анализ in silico, KNG1, редкий синонимичный вариант

ASSESSING THE IMPACT OF A RARE SYNONYMOUS VARIANT IN THE *KNG1* GENE ON THE DEVELOPMENT OF HEREDITARY ANGIOEDEMA

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Abstract. The main cause of edema in hereditary angioedema (HAE) is due to elevated bradykinin levels, caused either by C1-INH deficiency/change in functional activity and caused by mutations in the *SERPING1* gene or by mutations in the *F12, PLG, ANGPT1, KNG1, MYOF* and *HS3ST6* genes with a normal level and functionality of the C1-esterase inhibitor. The aim of the work was *in silico* prognostic analysis of the rare synonymous variant NC_000003.12:g.186725098T>C in the *KNG1* gene and its impact on the development of HAE symptoms. The material was a whole blood sample obtained from a woman with clinical manifestations of hereditary angioedema without a decrease in the levels and function of the C1 inhibitor. The research methods included whole exome sequencing, bioinformatic analysis of the *KNG1* gene mutation using a number of databases and web resources. Results. When processing full-exome sequencing data, we detected a synonymous variant in the *KNG1* gene (exon 4, isoform 1): NC_000003.12:g.186725098T>C. The patient is a heterozygous carrier of the variant, with a frequency of 0.000004 (1:264690). Presumably, the identified variant can lead to the development of sporadic edema through several pathways that are associated with the formation of bradykinin or its analogues. Therefore, (1) the mutant high-molecular-weight kininogen is more easily activated by kallikrein and becomes a source of bradykinin formation through the kallikrein-kinin system; (2) the mechanism of bradykinin formation undergoes significant changes and results in the formation of functionally active but aberrant bradykinin, which alters its inactivation by enzymes with a consequent increase in its half-life, (3) the changes in positions 380-389 bring about modifications in Lys-bradykinin reproduction such that in subsequent steps it is "easily" cleaved to bradykinin by arginine aminopeptidase. The results of our study therefore indicate a possible role of the identified variant in the *KNG1* gene in the development of HAE.

Keywords: primary immunodeficiencies, hereditary angioedema, mutation pathogenicity analysis, in silico analysis, KNG1, rare synonymous variant

Introduction

Hereditary angioedema (HAE) is a rare autosomal disease classified as an orphan disease. Episodes of the disease are accompanied by a varied clinical course, always characterized by sporadic swelling of the subcutaneous and submucosal tissues, blocking the normal flow of lymphatic fluid or blood in different parts of the body: limbs, face, gastrointestinal tract, respiratory tract [11, 14]. The exact incidence and prevalence of HAE is unknown but is estimated to be between 1:10 000 and 1:150 000 per population [7, 9, 10], with a higher incidence in females, as estrogen, changes in hormonal status, contraception, etc. can be a trigger [5].

There is wide variability in the kinetics of attacks, with some attacks occurring rapidly and others lasting 5 days or more. Laryngeal edema is particularly dangerous, as it can lead to asphyxia; on average, 1 death per 20 HAE patients occurs [9]. In addition, untimely treatment of a choking attack can lead to permanent brain damage, blindness, and limb paralysis [2]. The problems with edema are related to the fact that the mechanisms of edema development are not related to an allergic reaction, and taking antihistamines/corticosteroids has no therapeutic effect, and that specific therapies are very limited (purified human C1-INH concentrate, tranexamic acid, danazol).

The main cause of edema in HAE is usually due to elevated bradykinin (BK) levels, caused either by C1-INH deficiency and caused by mutations in the *SERPING1* gene or by mutations in the *F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF* and *HS3ST6* genes [1, 4, 7, 12, 13]. More than 450 HAE-causing mutations are linked to the *SERPING1* gene [4] and cause deficiency or malfunction of C1 inhibitor, these mutations account for 85% of all HAE cases. The alterations observed result in uncontrolled activity of plasma kallikrein and F12a, and high production of bradykinin (BK). Consequently, the permeability of the vascular walls is disturbed and fluid accumulates in the tissues thus creating prerequisites for sporadic edema.

Mutations in genes *F12*, *PLG*, *ANGPT1*, *KNG1* are associated with activation of kallikrein-kinin system, which is characterized by complex biochemical cascades, disturbances in which lead to development of localized edema. The pathophysiological changes caused by mutations in these genes are well understood, although new mutations associated with HAE can be identified. For example, mutations in the *HS3ST6* and *MYOF* genes have recently been identified showing that VEGF-mediated signal transduction is involved in the pathophysiology of the disease.

The identification of new mutations that may play a role in the pathogenesis of HAE and the development of genetic screening is an important step in understanding and treating the disease. Genetic testing for a few mutations remains one of the most informative methods to confirm the diagnosis of HAE. However, it is not always positive because only a small proportion of genetic abnormalities are considered to be conclusive evidence for the disease.

In some cases where the diagnosis is still in doubt, biological material obtained from a patient can be sent for full-exome sequencing. However, despite the possibility of obtaining a large body of mutation data with which to operate, evaluation or analysis of the effect of specific mutations or combinations of mutations on the organism remains a significant challenge. A similar situation is observed when analyzing mutations in genes directly linked to HAE, especially in HAE with mutations in *KNG1*.

It is for this reason that the application of bioinformatic analysis (*in silico* analysis), which includes a large arsenal of web-based applications aimed at assessing the impact of a mutation on a protein, has recently gained increasing interest [3, 12, 13]. This approach not only allows us to narrow down the genes but also the mutations that can provoke swelling in HAE.

Aim. *In silico* prognostic analysis of the rare synonymous variant NC_000003.12:g.186725098T>C in the *KNG1* gene and its impact on the development of HAE symptoms.

Materials and methods

We used a whole blood sample obtained from a 45-year-old patient who had spontaneous edema of unclear etiology since the age of 22. All procedures of the ethical standards of the institutional and/or international committee on research ethics and the Helsinki declaration of 1964 and its subsequent amendments or revisions of the ethical standards were followed. The study was conducted with the consent of the patient. The design of the study was approved by the local ethics committee of the St. Petersburg Pasteur Institute.

The DNA was isolated using a RIBO-PREP kit (CRIE, Moscow) from leucocyte rings. Concentration of DNA was determined using a Qubit dsDNA HS Assay Kit (Thermo Fisher Scientific Inc.). The quality of DNA was assessed using an Agilent 2100 Bioanalyzer capillary electrophoresis system (Agilent

Technologies Inc., USA). Full-exome sequencing was performed according to the manufacturer's protocol on the Illumina MiSeq platform. Bioinformatic analysis of the identified variant was done using the web application MutationTaster2021 (ENST00000265023) and included pathogenicity assessment and protein repositioning data [15]. Additionally, UniProt, ProteinAtlas, NCBI and PubMed databases were used in this study.

Results and discussion

Clinical data

In a 45-year-old woman from the age of 22 to the present, spontaneous swelling of the legs and hands periodically occurs. In recent years, the face sometimes swells, and abdominal pain syndrome is noted. The frequency of occurrence of edema is 1-2 times in 2-3 months, more often in the cold season. Angioedema triggers are severe frost, stress, overwork or psychoemotional stress. Regression of angioedema occurs independently within a few hours and up to 1.5 days. Therapy with antihistamines in a standard and double dose, or parenteral administration of glucocorticoids are without effect. Previously, for diagnostic purposes, a laboratory examination was carried out to determine the level and activity of the C1 inhibitor, as well as the level of the C4 complement component. The quantity and/or functional activity of these analytes were within normal limits. A search for mutations in the *SERPINGI* gene was carried out: as a result of Sanger sequencing of all exons (1-8) and the region of exon-intron junctions of the SERPINGI gene, pathogenic or probably pathogenic mutations were not detected. The characteristic features of the disease anamnesis, clinical manifestations, and the results of laboratory examinations served as the basis for continuing the diagnostic search.

When processing full-exome sequencing data, we detected a synonymous variant in the *KNG1* gene (exon 4, isoform 1): NC_000003.12:g.186725098T>C (NP_001095886.1:p.Pro134=, rs1560063067). Thymine and cytosine substitutions are characteristic of this variant. The patient is a heterozygous carrier of the variant, which according to TOPMED occurs with a frequency of 0.000004 (1:264690). However, this synonymous variant does not have any pathogenicity data and is not labelled in the ClinVar database.

Analysis of the variant performed using MutationTaster2021 showed that the variant is pathogenic because of changes affecting the splicing site. Hence, the variant causes a slight increase in the gDNA acceptor site at position 7815 (estimate: original variant 0.7044, mutant variant 0.7559) and an increase at position 7816 (estimate: original variant 0.56/mutant variant 0.68). Moreover, changes affect the donor site at position 7823 (score: 0.47). Interestingly, this synonymous variant in the cDNA shows no changes in the stop codon (position 2147) and ATG start position (213). However, the observed substitution of nitrogenous bases affects a large number of protein positions (Table 1).

In particular, a loss of function is possible at positions 28 to 132 (cystatin kininogen domain) and at positions 120 to 628, among which positions 379-380/389-390 (where kallikrein cleavage occurs), 380-389 (responsible for Lys-bradykinin formation) and 381-389 (responsible for bradykinin formation) are particularly prominent.

Since bradykinin is a well-known mediator of HAE symptoms, we hypothesis that the identified variant in the *KNG1* gene leads to alterations in bradykinin release. Production of bradykinin occurs in a complex cascade of events and starts with hydrolysis of high molecular weight kininogen (HMWK) by plasma kallikrein or tissue kallikreins. Activation by kallikrein ultimately leads to the formation of the biologically active peptides BK and Lys-BK, which can further produce desArg9-BK and Lys-desArg9-BK when cleaved by kininase I.

In the following events, these kinins (BK, Lys-BK, desArg9-BK and Lys-desArg9-BK) exert their action via two different receptors: receptor bradykinin B1 (BKRB1) and receptor bradykinin B2 (BKRB2). It is activated by BKRB2 when it contacts BK and Lys-BK, while desArg9-BK and Lys-desArg9-BK activate BKRB1. Both the binding of BK and Lys-BK to BKRB2 and the binding of desArg9-BK and Lys-desArg9-BK to BKRB1 on endothelial cells leads to increasing vascular permeability [6, 8]. In *KNG1* gene variant leading to HAE, bradykinin release is higher than physiological levels and is associated with changes in the positions involved in its release.

Our analysis *in silico* of the identified synonymous variant revealed that the changes observed in the nitrogenous base substitution affect important positions involved in bradykinin formation: 379-380/389-390, 380-389 and 381-389. Presumably, the identified variant can lead to the development of sporadic edema through several pathways that are associated with the formation of bradykinin or its analogues.

Therefore, (1) the mutant high-molecular-weight kininogen is more easily activated by kallikrein and becomes a source of bradykinin formation through the kallikrein-kinin system; (2) the mechanism of

TABLE 1. CHANGES IN KNG1 PROTEIN UNDER THE CONDITIONS OF THE NP_001095886.1:p.Pro134= MUTATION ACCORDING TO MutationTaster2021 data

Start (AA)	End (AA)	Feature	Details	Effect
28	**132**	DOMAIN	Cystatin kininogen-type 1	might get lost (downstream of altered splice site)
120	**153**	REGION	O-glycosylated at one site only	might get lost (downstream of altered splice site)
142	**142**	DISULFID		might get lost (downstream of altered splice site)
145	**145**	DISULFID		might get lost (downstream of altered splice site)
151	**254**	DOMAIN	Cystatin kininogen-type 2	might get lost (downstream of altered splice site)
169	**169**	CARBOHYD	N-linked (GlcNAc...)	might get lost (downstream of altered splice site)
205	**205**	CARBOHYD	N-linked (GlcNAc...)	might get lost (downstream of altered splice site)
206	**206**	DISULFID		might get lost (downstream of altered splice site)
218	**218**	DISULFID		might get lost (downstream of altered splice site)
229	**229**	DISULFID		might get lost (downstream of altered splice site)
248	**248**	DISULFID		might get lost (downstream of altered splice site)
264	**264**	DISULFID		might get lost (downstream of altered splice site)
267	**267**	DISULFID		might get lost (downstream of altered splice site)
273	**376**	DOMAIN	Cystatin kininogen-type 3	might get lost (downstream of altered splice site)
294	**294**	CARBOHYD	N-linked (GlcNAc...) (complex)	might get lost (downstream of altered splice site)
311	**311**	CONFLICT	V -> A (in Ref. 3; BAF83528)	might get lost (downstream of altered splice site)
326	**326**	MOD_RES	Phosphothreonine	might get lost (downstream of altered splice site)
327	**327**	MOD_RES	Phosphothreonine	might get lost (downstream of altered splice site)
328	**328**	DISULFID		might get lost (downstream of altered splice site)
329	**329**	MOD_RES	Phosphoserine	might get lost (downstream of altered splice site)
332	**332**	MOD_RES	Phosphoserine	might get lost (downstream of altered splice site)
340	**340**	DISULFID		might get lost (downstream of altered splice site)
351	**351**	DISULFID		might get lost (downstream of altered splice site)
370	**370**	DISULFID		might get lost (downstream of altered splice site)
376	**389**	PEPTIDE	T-kinin. / FTId=PRO_0000372485	might get lost (downstream of altered splice site)
379	**380**	SITE	Cleavage; by kallikrein	might get lost (downstream of altered splice site)
380	**389**	PEPTIDE	Lysyl-bradykinin. / FTId=PRO_0000006687	might get lost (downstream of altered splice site)
381	**389**	PEPTIDE	Bradykinin. / FTId=PRO_0000006688	might get lost (downstream of altered splice site)
383	**383**	MOD_RES	4-hydroxyproline; partial	might get lost (downstream of altered splice site)
389	**390**	SITE	Cleavage; by kallikrein	might get lost (downstream of altered splice site)
401	**401**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)

Table 1 (continued)

Start (AA)	End (AA)	Feature	Details	Effect
420	**449**	REPEAT		might get lost (downstream of altered splice site)
420	**510**	COMPBIAS	His-rich	might get lost (downstream of altered splice site)
431	**434**	PEPTIDE	Low molecular weight growth-promoting factor. / FTId=PRO_0000006690	might get lost (downstream of altered splice site)
450	**479**	REPEAT		might get lost (downstream of altered splice site)
480	**510**	REPEAT		might get lost (downstream of altered splice site)
533	**533**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
542	**542**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
546	**546**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
557	**557**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
571	**571**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
577	**577**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)
593	**593**	CONFLICT	I -> T (in Ref. 5; AAO61092 and 11; AA sequence)	might get lost (downstream of altered splice site)
614	**614**	DISULFID	Interchain (between heavy and light chains)	might get lost (downstream of altered splice site)
628	**628**	CARBOHYD	O-linked (GalNAc...)	might get lost (downstream of altered splice site)

bradykinin formation undergoes significant changes and results in the formation of functionally active but aberrant bradykinin, which alters its inactivation by enzymes with a consequent increase in its half-life, (3) the changes in positions 380-389 bring about modifications in Lys-bradykinin reproduction such that in subsequent steps it is "easily" cleaved to bradykinin by arginine aminopeptidase.

Conclusion

The results of our study therefore indicate a possible role of the identified variant in the *KNG1* gene in the development of HAE. Additionally, the findings also underscore the importance of further studies of synonymous variants in the *KNG1* gene, which may shed light on the etiology of the disease.

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