# ASSOCIATION OF COMPLEMENTFACTOR H GENE (CFH) SINGLE NUCLEOTIDE POLYMORPHISM WITH RECURRENT APHTHUS STOMATITIS

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## ABSTRACT

**Background:** Recurrent aphthous stomatitis (RAS) is a common chronic inflammation affecting oral mucosa that lead to mucosal ulceration. The causes are unclear, but dysregulation of the immune response has been proposed to be implicated in the development of the disease. In this study, we hypothesized that RAS is provoked by the dysregulation of the complement system, through the impairment of the function of complement regulatory proteins, the present study has aimed to investigate the impact of *CFH* gene SNPs that encodes the production of complement factor H in RAS development.

**Subject and Methods:** Blood samples from 46 patientswith recurrent aphthus stomatitis were collected including 35 males and 11 females and 46 age and sex matched apparently healthy (with healthy oral cavity) volunteersincluding 23 males and 23 females were involved as a control group. Gnomic DNA was extractedfrom each blood sampleusing the isopropanol/ethanol method. Specific primers were used to amplify the CFH gene fragment that harbors the rs1061170 site encoding theTyr402 aminoacid. The PCR products were digested with *Nla*III restriction enzyme.

**Results:** A significant difference was found between the age groups among the RAS patients in regard to the severity of and recurrence of the RAS episodes, it was found to be higher significantly among the age group (20-30 years) compared to other age groups among RAS patients. Out of the 46 RAS patients, the *CFH* single nucleotide polymorphism (SNP), Tyr402His polymorphism variant was detected in 18 (39.1%); 11 (23.9%) females and 7 (15.2%) males, represented as 8 (17.4%) Tyr/His heterozygous variants and 10 (21.7%) were His/His homozygous variant. Among the 46 healthy control group, the *CFH* single nucleotide polymorphism (SNP), (Tyr402His polymorphism variant) was detected in 6 (13%) all of them were Tyr402His variant, 2 (4.3%) males and 4 (8.7%) females. There was a significant difference in the *CFH* (Tyr/His, His/His) variants rates between the RAS group and the healthy control group ($p < 0.05$), but there was no significant difference of *CFH* (Tyr/His, His/His) variants rates between the males and females in the RAS group.

**Conclusions:** We suggest that Tyr402Hispolymorphism can be considered as a risk factor for the RAS development, and His204His variant is more associated with the disease, however, more studies are recommended to be conducted on a larger sample size to confirm these evidences.

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**Keywords:** Recurrent aphthus stomatitis, RAS, CFH, Tyr402His, oral mucosa

Recurrent aphthous stomatitis (RAS) is regarded as the most common ulcerative disease of the oral mucosa associated with painful rounded ulcers of erythematous margin and yellowish-gray pseudomembranous center. Also it occurs

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in otherwise healthy individuals and is typically located on the buccal and labial mucosa and tongue[1]. Diseases which also cause oral ulcers that may be mistaken for RAS include Behçet's disease, cyclic neutropenia, recurring intraoral herpes infections, HIV-related oral ulcers or gastrointestinal diseases such as Crohn's disease and ulcerative colitis[2]. About 20% of the population undergo episodes of RAS, and the evidence which depends on the ethnic and socioeconomic status ranges between 5% to 50%, such is based on the nature of the examined populations as well as on the methodology and design of the study[3].The second life decade (10-19 years of age) is regarded as the period in which the RAS occurrence peaks and the first episode starts in childhood. However, when the RAS begins or elevate in severity significantly during the third decade of age, the etiology of the episode might be attributed to an underlying disease or syndrome likehematologic, immunologic, connective tissue autoimmune disease, or even Behçet's syndrome[4].The etiologic factors of RAS ulcer are not well known and need to more explored, several factors are proposed to be implicated, many of them are local or systemic, like immunologic, hereditary, nutritional, and infectious agents in addition to some medications particularly the immunosuppressive drugs [5,6].As a predisposing etiologic factor, the abnormality in the immune response has taken a significant space in researching. It has been suggested that there are many immune-mediated responsesrelated to the development of RAS, including T lymphocytescytotoxicitytoward the oral epithelium, antibody-dependent cell-mediated cytotoxicity, and defects indifferent lymphocyte subpopulations[7]. One of the theories is that the damage might be induced by the deposition of immune complexes within the oral epithelium[8]. Immunologic response towards specific antigens of the oral mucosa has been found to provoke the aphthous stomatitis development[9]. The response takes place as a result of not proper initiation of cytokine cascade, that initiate othercertain immune mechanisms[9,10]. Furthermore, other reports haveemphasized on the role of the autoimmunity in developing the disease [11]. Factor H is regarded as one of the members of the complement system activation regulatory family which plays as a control protein of the complement system. It is a large (155 kilodaltons), soluble glycoprotein that circulates in human plasma, and found to regulate the complement system that has been activated through the alternative pathway, which ensures that the complement system does not cause the damage to the host tissues and only directed against the pathogens. Factor H protein controls the complement system activation on the surface of the host cells through the activity of cleavage C3b by cofactor Factor, and decay accelerating activity towards the alternative pathway C3-convertase C3bBb. The protection activity of factor H is exerted on host cells and surfaces but not on the surfaces of pathogens, because it binds to glycosaminoglycans (GAGs) which are normallyintegrated into thesecells' membranes but not the pathogen surfaces[12].

Aberrant factor H activity has been implicated in clinical manifestations[13,14].

Reduction in complement activity on pathogenic cells is due to overactive factor H leading to the increase in susceptibility to infections. Improper activity of factor H might leads to increased complement activity that develops autoimmune diseases. Therefore, it is expected that mutations andgeneticpolymorphisms in factor H probably result in pathologic conditions[15,16]. Furthermore, a single nucleotide polymorphism (SNP), Tyr402His, located in exon 9 of the CFH gene and representing a tyrosine to histidine change at amino acid position 402 in the CFH protein that alters the complement activity [17,18]. We hypothesized that RAS is provoked by the dysregulation of the complement system, through the impairment of the function of regulatory complement protein; we aimed at investigating the potential impact of *CFH* gene SNPs as a risk factor of RAS.

## MATERIAL AND METHODS

This case-control study has been conducted at Duhok medical research center (DMRC). The study population composed of 46 patients with RASincluding 35 males and 11 females and 46 apparently healthy individuals (including 23 males and 23 females)were involved as a control group. The study has been approved by the local ethical committee of the directorate of health at Duhok city, consent was provided by each participant. The oral clinical examination has been conducted by qualified oral medicine dentist, the medical history of patients was registered through a questionnaire. The RAS clinical picture was used for the diagnosis during the examination. The number of aphthae per flare-up and the frequency of recurrence was used to determine the severity of the disease (3 or less than 3; more than 3) as reported by the patients. The patients that have experienced a minimum of three episodes of RAS within past one year are included. Patients, under medication that could be associated with oral ulcers or *H. pylori* (such as antibiotics, proton pump inhibitors, H2 receptor blockers, Bismuth derivatives, non-steroidal anti-inflammatory drugs, chemotherapeutic agents, or vitamin supplements) for one month prior to the study, were excluded. Women during pregnancy and menstruation were excluded as well. Five milliliters of the venous blood has been collected from each subject, For *CFH* gene polymorphism, genomic DNA was extracted from peripheral blood collected withEDTA–anticoagulant by isopropanol method as described by[19]. The concentration of DNA was measured by Nano Drop spectrophotometer (Thermo Fisher). DNA was amplified using polymerase chain reaction (PCR) which was carried out on thermal cycler (Applied Biosystems, USA). PCR-restriction fragment length polymorphism (PCR-RFLP) was used for the genotyping of *CFH* as presented by Nada *et al*(2015), with minor modification and optimization[20]. Briefly the primer pair of CFH-F (5′- ACT GTG GTCTGC GCT TTT G-3′) and CFH-R (5′- TTT TTG GAT GTT TATGCA ATC TT-3′) was used to amplify the 244-bp DNA fragment that includes the (rs1061170) variant site. The PCR was performed in a 25 µl reaction mixture containing 200 ng genomic DNA, 12.5 µl master mix using Hot-Star-Taq Green DNA Polymerase (250 units), 5 ρmol each forward and reverse primers.

The thermal cycles were: initial denaturation of 94ºC for 5 minutes; 35 cycles of 94ºC for 30 seconds; 62ºC for 30 seconds; 72ºC for 35 seconds; and a final extension at 72ºC for 5 minutes. The 244-bp PCR fragments were digested by *Nla*III restriction enzyme (Thermo Scientific) at 37ºC for 2-4 hours. The digested fragments have been separated and visualized on 2% agarose gel in a UV illumination chamber.

## STATISTICAL ANALYSIS

The statistical package for the social sciences (SPSS) was used in the data analyses. The difference of CFH genotypes distribution was tested by Chi Square test. The CFH genotype association with the risk of RAS was estimated by odds ratio (OR) and 95% confidence interval (95% CI). *P* value (< 0.05) was regarded significant.

## RESULTS

In the present study; 92 individuals were enrolled and divided in to two groups: the first group was the study group which composed of 46 patients with RAS disease, consisting of 11 females (23.91%) and 35 males (76.08%), their age range was (15-40 years), the family history of RAS disease was positive for 24 patients (52.17%). The second group was the control group which composed of 46 apparently healthy individuals, consisting of 23 females (50%) and 23 males (50%), their age range was (15-30 years), only one individual (2.173%) had had a family history of RAS disease. Among the RAS patients, the male rate was significantly higher compared to females ($p < 0.05$). A significant difference was found between the age groups among the RAS patients in regard to the severity of and recurrence of the RAS episodes, it was found to be higher significantly among the age group (20-30 years) compared to other age groups among RAS patients ($p < 0.001$). Based on information provided by the subjects involved in the study, the attack frequency of RAS per month was 1 - 4. Using primers specifically targeting the *CFH* gene flanking the 402 Tyr region, the PCR gave a DNA band of 244-bp. Digesting the PCR products with *Nla*III restriction enzyme produced a 244-bp single band for the CFH wild genotype 402 Tyr/Tyr, two bands of 161-bp and 83-bp respectivelyfor the 402 His/His homozygous polymorphic genotype and three bands of 83-bp, 161-bp and 244-bp for the 402 Tyr/His heterozygous polymorphic genotype as shown in the Figure 1 bellow.

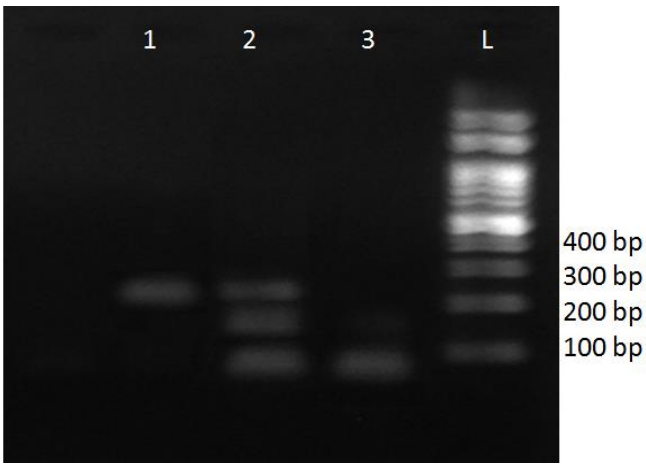


**Figure1. PCR- RFLP analysis: Agarose gel electrophoresis (2%) shows the DNA fragments of the CFH gene PCR products and the Tyr402His polymorphism of CFH. Lane 1; 244 bp evidence of Tyr204Tyr wild not mutated genotype, lane2; 244, 161 and 83 bp DNA fragments evidence of Tyr402His heterozygous variant, lane 3; 161 and 83 bp DNA fragments indicating the Tyr402His homozygous genotype, lane L; a 1000 bp DNA ladder.**

Out of the 46 RAS patients, the *CFH* single nucleotide polymorphism (SNP), Tyr402His polymorphic variant was detected in 18 (39.1%); 11 (23.9%)

females and 7 (15.2%) males, represented as 8 (17.4%) Tyr/His heterozygous variants and 10 (21.7%) were His/His homozygous variant. Regarding the RAS patients age groups; in age group 10-20 years, 7 (15.2%) were Tyr402His mutated variants, 2(4.3%) of them were Tyr/His heterozygous variants and 5 (10.8%) of them were His/His homozygous variant. In age group 21-30 years, 4 (8.7%) were Tyr402His mutated variants, 2 (4.3%) of them were Tyr/His heterozygous variant, and the other 2 (4.3%) were His/His homozygous variants. In age group 31-40 years, 7 (15.2%) were Tyr402His mutated variants, 3 (6.5%) were Tyr/His heterozygous variants and 4 (8.7%) were His/His homozygous variants. Among the 46 healthy control group, the *CFH* single nucleotide polymorphism (SNP), (Tyr402His mutated variant) was detected in 6 (13%) all of them were Tyr204His variant, 2 (4.3%) males and 4 (8.7%) females (Table 1 and 2).

**Table 1: Frequency of CFH Tyr402His SNP variants among RAS patients and controls**

| Genotype | RAS patients (*n*=46) *N* (%) | Healthy controls (*n*=46) *N* (%) | OR (95% CI) |
|---|---|---|---|
| Tyr204Tyr (wild) | 28 (60.9) | 40 (86.96) | 4.2 (1.17–4.929) |
| Tyr204His | 8 (17.4) | 6 (13) | |
| His204His | 10 (21.7) | 0 (0) | |

(*p*= 0.04)

**Table 2: Frequency of CFH Tyr402His SNP variants among RAS patient's age groups**

| Age group (Yeas) inRAS patients | Tyr204His SNP *N* (%) | Tyr204His variant *N* (%) | His204His variant *N* (%) |
|---|---|---|---|
| 10-20 | 7 (15.2) | 2 (4.3) | 5 (10.8) |
| 21-30 | 4 (8.7) | 2 (4.3) | 2 (4.3) |
| 31-40 | 7 (15.2) | 3 (6.5) | 4 (8.7) |
| Total | 18 | | |

Using the Chi Square test to analyze the difference of *CFH* genotypes distribution, there was a significant difference in the *CFH* (Tyr/His, His/His) variants rates between the RAS group and the healthy control group ($p < 0.05$). There was no significant difference of *CFH* (Tyr/His, His/His) variants rates between the males and females in the RAS group, also there was no significant difference of *CFH* (Tyr/His, His/His) variants rates between the age groups in RAS group. The odd ratio (OR) and 95% and confidence interval (95% CI) was used to estimate the correlation between the RAS and the *CFH* (Tyr/His, His/His) polymorphic variants, it has been found that the *CFH* (Tyr/His, His/His) polymorphic variants are significantly correlated with RAS patients when compared with the healthy group ($p = 0.04$, OR = 4.2, 95% CI: 1.17–4.929), the strongest correlation was found with His/His genotype carriers ($r = 0.63$) and no significant correlation was found with Tyr/Tyr wild genotype (Table 2). Regression equation revealed that the risk of RAS is increased 3.82 times in individuals with *CFH* (Tyr/His, His/His) mutated variants compared to those with the wild *CFH* (Tyr/Tyr) genotype.

## DISCUSSION

Recurrent apthous stomatitis (RAS) is a common painful inflammatory ulcerative response of oral cavity mucosa. The exact etiology of RAS remains unclear in spite of the broad research. Several factors seem to have been implicated as etiologic factors and involved in the pathogenesis of RAS.The disruption of both humoral and cellular immune response may occur in patients with aphthae[21]. This disruption

leads to the development of aphthous ulcers in response to an enhanced immunologic reaction against the oral mucosa [22,23]. An abnormally initiated cascade of cytokines followed by the activation of certain immune processes leads to local tissue damage and inflammation[22,23,10]. The disruption of the immune system in RAS predisposed subjects occurs in response to some kind of undefined factors. This may include exposure to viral and bacterial antigens or to some food ingredients, stress or local trauma. Also the antibodies for different antigens of the epithelium found in RAS patients indicate the role of autoimmunization in the etiopathologic process[24].In the current study, we found that the rate of the RAS is significantly higher among males (76.08%) compared to females (23.91%), these results are in contrast to those reported by[25], they found that females (56.3%) were more frequently affected than males (43.7%) and this difference was statistically significant ($p<0.005$). Also the results in the current study were inconsistent results with the findings of Safadi[26]. However, the immune response of the females is more affected by the emotional situations and stress, and the hormonal changes in pregnancy and menstruation plays a significant role in altering the immune response and RAS episodes[27]. The controversy of RAS findings in the present study compared to others regarding the gender frequency might be due to the smaller sample size recruited in the current study that could not be a real representative of the population. Our study showed a significant difference between the age groups among the RAS patients in regard to the severity of and recurrence of the RAS episodes, it was found to be higher significantly among the age group (20-30 years) compared to other age groups among RAS patients ($p < 0.001$), denoting that the second decade of age is associated with higher risk of RAS. These results are in accordance with the findings of Davatchi*et al.*, (2008) in Iran[28], and Mustafa J. Abdullah (2013) in Sulaimani, Iraq[29], they indicated that the most commonly affected age group was 20-29 years and the prevalence decreased with aging. It has been assumed that the occupation status and the education might have a significant impact on the prevalence of RAS, as the educational and occupational level elevates the opportunity of getting the stress and anxiety increases as well, that's what is clearly observed during the students' exams. The complement system consists of a cascade of effective proteins leading to cell lysis[30]. Complement factor H (CFH) is crucial regulator in the complement system activation through the alternative pathway. Its' biological role is to inhibit the complement pathway response by binding to C3b and damaging the C3 convertase[31,32]. To the best of our knowledge, this is the first study to explore the CFH SNPs as a risk factor for the RAS. In the present study, we explored the impact of CFH Tyr402His single nucleotide polymorphism on the prevalence of RAS. We found that CFH Tyr402His polymorphism is significantly associated with RAS compared to healthy individuals ($p<0.05$), but there was no significant difference between the males and females among the RAS group. However, no data are published about the impact of the CFH Tyr402His single nucleotide polymorphism on RAS

development, but the link between the CFH Tyr402His variants and other diseases has been reported. Klein *et al* has found a strong link between a single amino acid variant in the (Tyr402His) of complement factor H and age-related macular degeneration (ARMD)[33]. It has been found the Dense deposit disease (membranoproliferative glomerulonephritis. type II) has a massive complement response through the alternative pathway in an uncontrolled process and impairment in controlling surface activation[34]. It has been assumed that CFH Tyr402His mutant has led to the reduction CFH affinity for C-reactive protein (CRP), which in turn might be involved the modulation of the alternative pathway complement response and effect via CFH binding[35], that's might leads to the continuous activation of the immune response of the oral mucosal layer, resulting in defects in the regulation of the alternative pathway of the complement response, recurrent and exaggerated inflammation, and oral mucosal damage because of the accumulation of the membrane attack complex (MAC) on the mucosal cell membranes[36].The results represented in the current study reveal a 3.82 fold increased risk of RAS in Tyr204His, His204His variants, but the strongest association was found between His204His variant carrier. In a study conducted by Sijia Cao *et al.*, 2016, they declared that CFH Y402H polymorphism is a known genetic risk factor of age-related macular degeneration (AMD). The contribution to the disease process may be through increased activation of the NF-κB pathways and upregulation of inflammasome genes. So in the case of RAS, the NF-κB pathway is expected to mediate the expression of proinflammatory mediators, including inflammasome products, thereby contribute to the local proinflammatory responses in the oral mucosa surfaces[37]. Based on the evidences obtained in this study, we suggest that Tyr402His polymorphic can be considered as a risk factor for the RAS development, and His402His variant is more associated with the disease, however, more studies are recommended to be conducted on a larger sample size to confirm these evidences.

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## پوختە

# گهورینێن تەخێن شانەیی یێن هەمەجور لدەف کوردێن عێراقێ یێن کو پەنجەشێرا خوینێ ژجورێ مایلویدا دژوار هەی. ڤەکولینەکا پاشڤەیێ لسەر 105 نەخوشان

**پێشەکی:** هەودانا دەڤی یا دووجارەکی هەودانەکا دوم درێژە کو مایتێکرنێ دکەت ل سەر تەخێن دەڤی ود بیتە ئەگەرێ سوربونا وان تەخا. ئەگەر نە دیارن لێ پێشبینی دهێتەکرن کو بەرسڤا سیستمێ بەرگریا لەشی ئێکە ژ وان ئەگەرا. مە پێشبینی کریە کو لاوازبونا کونترولکرنا سیستمی تامکەر یێ بەگریێ رولەکێ گرنگ یێ هەی د پەیدابونا نەخوشیێ دا ب رێکا نە کارکرنا فاکتەرێ تەمامکەر H.

**رێکێن ڤەکولینێ:** ئەڤێ ڤەکولینێ 46 نەخوشێن هەودانا دەڤی یا دووجارەکی ب خوڤە گرتیە, 35 نێر و 11 مێ, و 46 خوبەخش , 23 نێر و 23 مێ. سامپلێن خوینێ ژ هەمیا هاتنە وەگرتن وترشێ نیوکلیوتیدی ژێ هاتە جوداکرن, PCR هاتە بکار ئینان ژ بو مەزن کرنا جینێ فاکتەرێ تامکەر Hو پاشی هاتە هەرسکرن بریّکا NlaIIIئەوێ وترشێ نیوکلیوتیدی هەرس دکەت.

**ئەنجام:** جوداهی هاتە دیتن دناڤ بەرا تەخێن تەمەنی یێن نەخوشێن نەخوشێن هەودانا دەڤی یا دووجارەکی سەبارەت دژواری و دوجارەبونا نەخوشیێ. دیار بو نەخوشی دوبترە دبیت دناڤ تەخا نەخوشا یێن (20–30 ) سالی دا. دناڤ 46 نەخوشان دا , Tyr402 His هاتە دیتن دگەل 18 (39.1٪), 11 (23.9٪) مێ و 7 (15.2٪) نێر. و 8 (17.4٪) Tyr402Hisنە وەك هەڤیا زایکوتی، و 10 (21.7٪) کان His 402Hisوەك هەڤیا زایکوتی. دناڤ 46 گروپێ ساخلەم ،جوراوبونانیوکلیوتیدی Tyr402Hisهاتە دیتن دناڤ 6 (13٪)کەسان دا و هەمی ژ جورێTyr204Hisنە وەك هە ڤیا زایکوتی، 2 (4.3٪) نێر و 4 (8.7٪) مێ. جوداهیەکا دیار هەبو سەبارەت (Tyr402His ، His 402His) دناڤبەرا گروبێ نەخوشان و گروبێ ساخلەما (p<0.05). لێ جوداهیەکا بەرچاڤ نەبو سەبارەت (Tyr402His ، His 402His) دناڤبەرا نێر و مێادا ل گروپێ نەخوشا.

**دەرئەنجام:** گوهرینا Tyr204Hisل جینێ CFH دبیت بهێتە هەژمارتن وەك فاکتەرەکێ ترسناکیێ بو پەیدابونا نەخوشیّا هەودانا دەڤی یا دووجارەکی و His204Hisوەك هەڤیا زایگوتی پتر یا گرێدایە ب نەخوشیێ ڤە.

## الخلاصة


### تأثير اضافة جرع مختلفة من الدكساميثازون الى البوبيفكائيين في العمليات القيصرية باستخدام التخدير داخل القراب

**الخلفية والأهداف:** ألتهاب الفم القلاعي المتكرر هو التهاب مزمن شائع يؤثر على الغشاء المخاطي للفم الذي يؤدي إلى تقرح الغشاء المخاطي. الأسباب غير واضحة، ولكن من المعتقد أن الاستجابة المناعية قد تكون مسؤولة عن تطور المرض. في هذه الدراسة، افترضنا أن المرض ينتج عن استفزاز من قبل ضعف تنظيم فاعليةالنظام المناعي المكمل، من خلال ضعف وظيفة البروتين التنظيمي التكميلي. في هذه الدراسة كان الهدف هو التحقق من تأثير الأشكال الجينية المتباينة للجين الذي يشفر إنتاج عامل المناعة التكميلي Hعلى نشؤ المرض.

**طرق البحث:** تضمنت الدراسة مجموعة مكونة من 46 مريضا مصابا بالتهاب الفم القلاعي المتكرر، بينهم 35 ذكور و 11 إناث و 46 متطوعا أصحاء كمجموعة مقارنة (لا يعنون من أية مشاكل صحية في الفم) من بينهم 23 ذكور و 23 من الإناث. جمعت عينات الدم من كل منهم، وتم استخراج الحمض النووي الجيني باستخدام طريقة الأيزوبروبانول / الإيثانول. واستخدمت طريقة تفاعل البلمرةالتسلسلي لتضخيم جزء الجينيشفر إنتاج عامل المناعة التكميلي Hوالذي يؤوي موقع rs1061170 ويشفر موقع الحامض الأميني Tyr402. تم تقطيع نواتج تضخيم الحامض الأميني بأستخدام انزيم NlaIII ألهاضم للحامض النووي .

**النتائج:** تم العثور على فرق معنوي بين الفئات العمرية لدى مرضى التهاب الفم القلاعي فيما يتعلق بشدة وتكرار نوبات المرض، فقد وجد أن المرض يتكرر بصورة أعلى بكثير بين الفئة العمرية (20-30 سنة) مقارنة مع الفئات العمرية الأخرى بين المرضى. من أصل 46 مرضى ، تم الكشف عن تعدد الأشكال النيوكليوتيدية المتباينةTyr402 His في 18 (39.1٪), 11 (23.9٪) من الإناث و 7 (15.2٪) من الذكور، و 8 (17.4٪) Tyr402His متغايرةالزايكوت، و 10 (21.7٪) كان His 402His متماثل الزايكوت. ومن بين 46 مجموعة السيطرة الصحية، تم الكشف عن تعدد الأشكال النكليوتيدات (Tyr402His في 6 (13٪) وكان جميعهم يحملون Tyr204His المتباينة الزايكوت، 2 (4.3٪) من الذكور و 4 (8.7٪) من الإناث. كان هناك فرق معنوي في معدلات المتغيرات (Tyr402His ، His 402His) بين مجموعة المرضى ومجموعة المقارنة (p<0.05). ولكن لم يكن هناك فرق معنوي في معدلات المتغيرات (Tyr402His ، His 402His) بين الذكور والإناث في مجموعة المرضى.

**الاستنتاجات :** يمكن اعتبارطفرة Tyr204His في مورثة CFH عامل خطورة لظهور مرضى التهاب الفم القلاعي ، و His204His المتماثل الزايكوت هو الأكثر أرتباطا بهذا المرض، ومع ذلك، يوصى بإجراء المزيد من الدراسات على عينة أكبر من المرضى لتأكيد هذه الأدلة.