# Clinical Spectrum and Geographic Distribution of Keratitis Fugax Hereditaria Caused by the Pathogenic Variant c.61G>C in *NLRP3*

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• PURPOSE: To chart clinical findings in individuals with keratitis fugax hereditaria (KFH) and the geographic distribution of their ancestors.
• DESIGN: A prospective cross-sectional study.
• METHODS: This study took place in a tertiary referral center with a cohort of 84 Finnish patients (55% female) from 25 families with the pathogenic nucleotide-binding domain, leucine-rich repeat (NLR) family pyrin domain containing 3 (*NLRP3*) variant c.61G>C. Observation procedures and main outcome measures were Sanger sequencing, clinical examination, corneal imaging, and a questionnaire regarding symptoms, quality of life, treatment, and comorbidities.
• RESULTS: The oldest members in each family were born in Ostrobothnia in Western Finland or in Southwestern Finland with historical ties to Sweden. One carrier was asymptomatic. Most (77%, 46/60) experienced their first attack between age 6 and 20 years. Three-quarters had unilateral attacks 3 to 5 times annually, primarily triggered by cold wind or air, or stress. Eighty percent (48/60) reported ocular pain (median, 7 on scale 1-10), conjunctival injection, photophobia, foreign body sensation, and tearing during attacks. Visual blur occurred in 75% (45/60) and 91% (55/60) during and after the attack, respectively, for a median of 10 days (range, 1 day-2 months). Forty-seven percent (39/60) had corneal oval opacities with irregular tomography patterns and mild to moderate decrease (20/60 or better) in best-corrected visual acuity that improved with scleral contact lenses. Except for headache in 40%, systemic symptoms were absent during the attacks.
• CONCLUSIONS: Symptoms and signs of KFH are restricted to the anterior segment of the eye and vary widely between individuals. We recommend scleral contact lenses as the first-line treatment for reduced vision. Allele frequencies suggest that KFH goes unrecognized in Sweden and populations with Scandinavian heritage. (Am J Ophthalmol 2022;236: 309–318. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

In 1964, Olavi Valle, then a Finnish resident in ophthalmology, described in 10 members of 1 family a recurrent unilateral keratitis that he named keratitis fugax hereditaria (KFH, MIM 148200).[1] The second Finnish family was reported in 1987, whereupon the disease was renamed keratoendotheliitis fugax hereditaria[2] based on misinterpretation of specular endothelial microscopy findings.[3] We recently discovered in 23 affected Finnish families that this autosomal dominant disease is caused by a heterozygous pathogenic variant c.61G>C, p.(Asp21His) in the nucleotide-binding domain, leucine-rich repeat (NLR) family pyrin domain containing 3 (*NLRP3*) gene, and showed that endothelial cells were uninvolved.[3,4]

Unilateral ocular pain, conjunctival injection, photophobia, and tearing characterize the acute inflammatory attacks of KFH that last for 1 to 3 days and leave a blurry vision for several weeks.[1,2,4] Our confocal microscopy results suggest influx of leukocytes into the corneal stroma during the attack.[3] The attacks begin at the median age of 11 years and recur 1 to 6 times a year. Repeated attacks result in bilateral horizontally oval central stromal opacities in one-half of the patients that can reduce visual acuity.[3,4]

*NLRP3* encodes cryopyrin, a crucial member of the NLRP3 inflammasome.[5] Pathogenic variants in *NLRP3* cause rare autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS).[6] These include neonatal-onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome, and familial cold autoinflammatory syndrome.[6] They are characterized by excessive interleukin-1$\beta$ secretion that results in systemic autoinflammation.[7] Common symptoms include recurrent fever, headache, arthritis, urticaria-like rashes, hearing loss, and

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Accepted for publication October 23, 2021.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.10.025

conjunctivitis.[5,8] KFH is the fourth member of the CAPS family with apparently localized symptoms.[3,4]

The corneal phenotype of KFH is now well described,[1-4] but a full systematic documentation of the signs and symptoms, including potential mild systemic ones, is lacking. Here we chart and describe the symptoms and signs of KFH in 84 affected carriers of the common c.61G>C *NLRP* variant in 25 families, including 32 new patients from 10 new families. Moreover, we charted the geographic location of their ancestors. In addition to a clinical ophthalmologic examination, the patients completed a comprehensive questionnaire to chart their symptoms, quality of life, treatment, and comorbidities. Because other pathogenic variants in *NLRP3* cause divergent systemic autoinflammatory reactions, we paid special attention to any extraocular symptoms and manifestations. Understanding the full clinical spectrum of this corneal autoinflammatory disease will help ophthalmologists to recognize it.

## PATIENTS AND METHODS

All patients clinically diagnosed with KFH at the Helsinki University Hospital between April 3, 2016, and January 30, 2020, and verified to be carriers of the c.61G>C (rs200154873) *NLRP3* variant were eligible for the study. Every patient referred to us for a workup of KFH was invited to have a clinical examination and genetic analysis, and none of them refused. Family members were offered the same opportunity. For this study, in addition to the clinical examination, a paper questionnaire was mailed to all genetically confirmed patients. Patients were asked to complete the survey on their own and mail it back to the investigators before the due date. It was returned by two-thirds of them (60/84). We estimate that approximately 700 people in Finland have KFH based on allele frequency data (Supplemental Table 1),[9] of which 127 variant carriers have already been recognized.

The project was approved by the Hospital Region of Helsinki and Uusimaa Institutional Review Board and followed the tenets of the Declaration of Helsinki. All participants gave their written informed consent. The consent was given by the parent in case of pediatric patients.

• **GENETIC ANALYSIS:** The *NLRP3* variant c.61G>C (rs200154873; GenBank: NM_004895.4) was confirmed by Sanger sequencing as described earlier.[4] Variant allele frequencies were determined from Genome Aggregation Database (gnomAD) version 2.1.1.[9]

• **CLINICAL EXAMINATION:** A comprehensive clinical and genetic evaluation was performed (A.I. and J.T.) in all patients, except one of very advanced age (patient 1-14). It included personal history, review of patient medical records for reported symptoms and coexisting diseases, family history, a pedigree, best-corrected visual acuity (BCVA, Snellen), intraocular pressure (iCare IC100; Icare Finland Oy), and biomicroscopic examination. Corneal abnormalities were classified in 4 categories: none, mild stromal haze, central oval opacity, and multiple opacities (Supplemental Table 2). The cornea was imaged by Fourier domain, swept-source anterior segment optical coherence tomography (SS-1000 CASIA; Tomey).

• **QUESTIONNAIRE:** To chart potential systemic signs and symptoms, we used a questionnaire consisting of open-ended questions, multiple-choice questions, and scaled questions that were designed specifically to evaluate KFH as a type of CAPS. The questions covered 4 topics: personal information, eye health, general health, and symptoms (Supplemental Text 1, original questionnaire 10.5281/zenodo.5101477). Ocular pain and quality of life were rated on a scale from 1 (no pain/no impact on quality of life) to 10 (intolerable pain/maximal impact on everyday life).

• **STATISTICAL METHODS:** Data were analyzed with SPSS 25-v100 software (IBM Corp). Median with range and interquartile range (IQR) is reported for continuous variables. We used nonparametric tests to compare variables between groups. Characteristics between groups were compared using the Spearman rank correlation and Mann-Whitney *U* test. Level of significance was set at .05. All tests were 2-tailed.

## RESULTS

The study enrolled all 84 patients diagnosed with c.61G>C variant KFH at our hospital during the study period. Participants came from 25 families; 46 (55%) were female and 38 (45%) male ($P = .45$, binomial test). Seventy-seven patients (92%) had a family history of KFH. The remaining 7 (8%) had incomplete genealogy data. All participants were native Finns. Sixty patients (71%), of whom 36 (60%) were female and 24 male (40%), returned the questionnaire. Those who did not return the questionnaire (24 [29%]) did not differ systematically by age, sex, age of onset, number of attacks, visual acuity, and corneal opacity compared with the respondents. The age range of those who returned the questionnaire was 14 to 94 years (median, 54; IQR, 35-68 years).

• **GEOGRAPHIC DISTRIBUTION OF KFH ANCESTORS:** Excluding the capital region, the birthplaces of the oldest known members in each KFH family are located in Ostrobothnia in Western Finland or in Southwest Finland (Figure 1). These regions parallel the municipalities in which the population is officially Swedish speaking or bilingual with a Swedish-speaking majority. The allele frequency


**FIGURE 1. Geographic distribution in Finland of the birthplaces of the oldest known ancestors of keratitis fugax hereditaria patients in 25 families.**

of the c.61G>C variant in Sweden (0.011%) is nearly as high as in Finland (0.014%) based on the gnomAD database,[9] although to the best of our knowledge, no patients have yet been reported from Sweden. The variant has also been detected in the gnomAD population category "other," which means that the individuals did not cluster with the major populations in principal component analysis.[9]

• **AGE AT SYMPTOM ONSET:** The age at the time of the first attacks ranged from 2 to 55 years (median, 11; IQR, 9-15 years). Although 46 of the 60 patients (77%) experienced their first attack between age 6 and 20 years, 7 patients were younger and 7 were older at the time of first symptoms, and only 1 female respondent was older than 30 years at the onset of symptoms. Forty-five patients (75%) had 3 to 5 attacks per year (Figure 2, A). The maximum number of attacks was 10 per year in 2 patients (3%).

• **TRIGGERING FACTORS:** On the basis of the questionnaire, 39 patients (65%) reported environmental or other factors that triggered the acute attack, and 11 (18%) speculated about such factors. The most common presumed triggers were psychologic stress in 35 patients and cold wind and air in 26. Other reported triggering extrinsic and intrinsic factors are presented in a diagram (Figure 3). Two patients reported attacks in both eyes within an interval of a few days, and 28 (47%) reported mild symptoms at bedtime before their acute attack the next day.

• **SYMPTOMS DURING ACUTE ATTACKS:** Of the 60 patients who responded to the questionnaire, more than 80% (48/60) reported conjunctival injection, ocular pain, photophobia, foreign body sensation, and excessive tearing during acute attacks (Table 1). We found no evidence of differences between women and men during the acute attacks. However, the pain intensity varied by different age at onset (Figure 2, B and C). The overall highest median pain intensity was 7 on a scale from 1 to 10 (Figure 2, B). The pain lasted for 2 to 3 days (Figure 2, C).

Twenty-eight respondents (47%) felt better while having their eye closed during the acute attack; however, 14 patients (23%) preferred to keep it open, and 18 (30%) reported no difference. Forty-five patients (75%) reported reduced vision during the attack (Table 1), and 55 patients (91%) experienced blurriness after the acute symptoms (Figure 2, D). Two patients experienced blurriness only for 1 day, while 5 patients suffered from it for more than 2 months. When results were combined from all patients, the visual blur lasted a median of 10 days (range, 1-50; IQR, 3-25 days) between the ages of 21 and 60 years, but was reported to be shorter (3-5 days) when aged younger than 20 years. It should be noted that 1 carrier (1.2%; 95% CI, 0%-6%) of the pathogenic variant had not experienced any symptoms by the age of 67 years.

• **CORNEAL OPACITIES AND VISUAL ACUITY:** Altogether, 39 (47%) of the 83 clinically examined patients had a corneal opacity (46% of females 55% of males; $P = .51$, Fisher exact test). The BCVA of 62 patients (75%) was at least 20/20 in the eye with better visual acuity, 7 (8%) had a BCVA of less than 20/40, and 2 patients (2%) less than 20/60 (Supplemental Table 2). All patients with a BCVA of less than 20/40 had typical KFH-related central corneal opacities. In addition, 1 individual each had a history of central serous chorioretinopathy, optic neuritis, and penetrating keratoplasty. Thirty eyes with a central oval opacity and 5 eyes with a mild stromal haze had 20/20 vision or better.

Seventy-five patients (89%) underwent swept-source anterior segment optical coherence tomography, of which 70 (83%) could be assigned in the analysis in 2 groups (clear

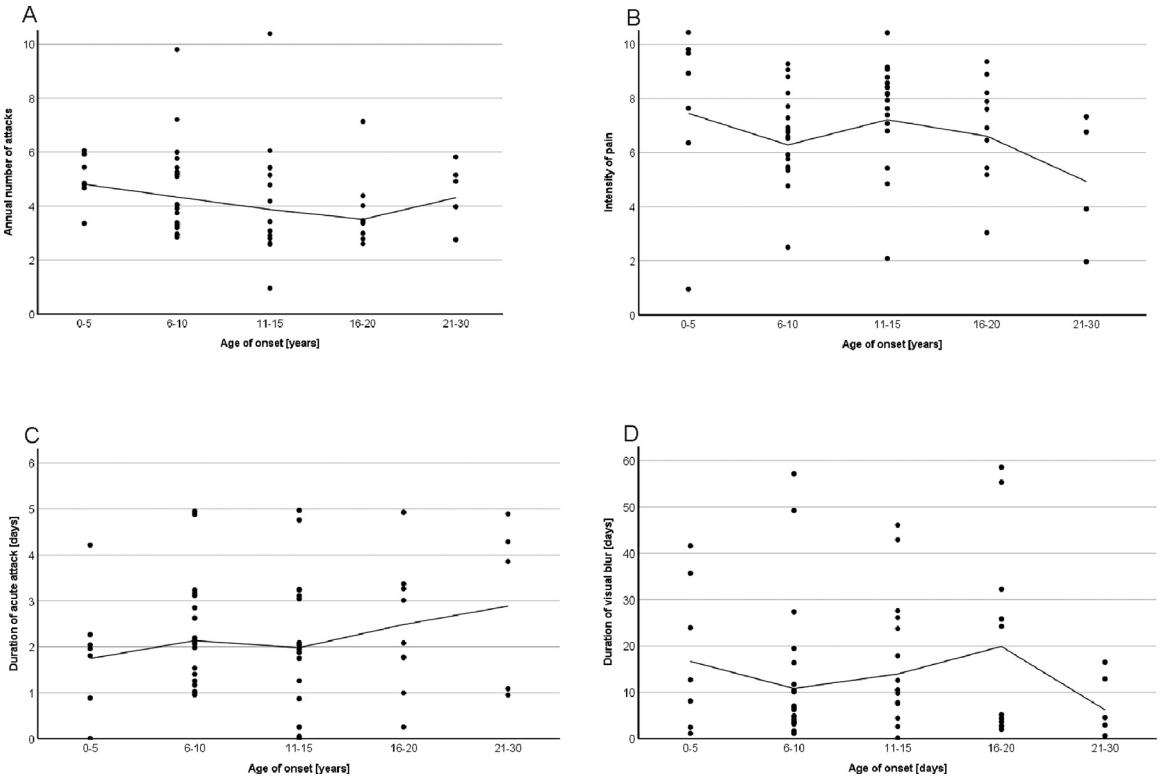


**FIGURE 2.** (A) The median number of attacks per year, (B) the median intensity of ocular pain during the acute attack (scale: 1 no pain and 10 intolerable pain), (C) the median duration of acute attack in days, and (D) the median duration of blurry vision after the acute attack in days by the age of onset in 60 patients with keratitis fugax hereditaria.

**TABLE 1.** Symptoms During Acute Attacks

| Symptom | Total ($N = 60$) | Females ($n = 36$) | Males ($n = 24$) | Aged <40 Years ($n = 19$) | Aged ≥40 Years ($n = 41$) |
|---|---|---|---|---|---|
| Ocular symptoms | | | | | |
| Red eye/conjunctival injection | 59 (98) | 36 (100) | 23 (96) | 19 (100) | 40 (98) |
| Eye pain | 56 (93) | 36 (100) | 20 (83) | 17 (89) | 40 (98) |
| Photophobia | 55 (92) | 33 (92) | 22 (92) | 18 (95) | 37 (90) |
| Foreign body sensation | 51 (85) | 33 (92) | 18 (75) | 18 (95) | 33 (80) |
| Watery eyes/excessive tearing | 51 (85) | 34 (94) | 17 (71) | 18 (95) | 33 (80) |
| Glare | 46 (77) | 30 (83) | 16 (67) | 9 (47) | 36 (88) |
| Reduced vision | 45 (75) | 30 (83) | 15 (63) | 11 (58) | 34 (83) |
| Light scattering | 31 (52) | 22 (61) | 9 (38) | 9 (7) | 20 (49) |
| Eyestrain | 31 (52) | 22 (61) | 9 (38) | 10 (53) | 21 (51) |
| Burning sensation | 22 (37) | 18 (50) | 4 (17) | 6 (32) | 16 (39) |
| Diplopia | 22 (37) | 17 (47) | 5 (21) | 5 (26) | 18 (44) |
| Itchy eye | 21 (35) | 16 (44) | 5 (21) | 9 (47) | 13 (32) |
| Eyelid swelling | 18 (30) | 15 (42) | 3 (13) | 4 (44) | 14 (34) |
| Shadows in vision | 11 (18) | 7 (19) | 4 (17) | 3 (16) | 8 (20) |
| Eye discharge | 10 (17) | 7 (19) | 3 (13) | 3 (16) | 8 (20) |
| Sensation of crying | 1 (2) | 1 (3) | 0 | 0 | 1 (2) |
| Nonocular symptoms | | | | | |
| Fever | 3 (5) | 2 (6) | 1 (4) | 1 (5) | 2 (5) |
| Other (pulsating pain, chills) | 3 (5) | 3 (8) | 0 | 0 | 3 (7) |

Note: Data are presented as *n* (%).

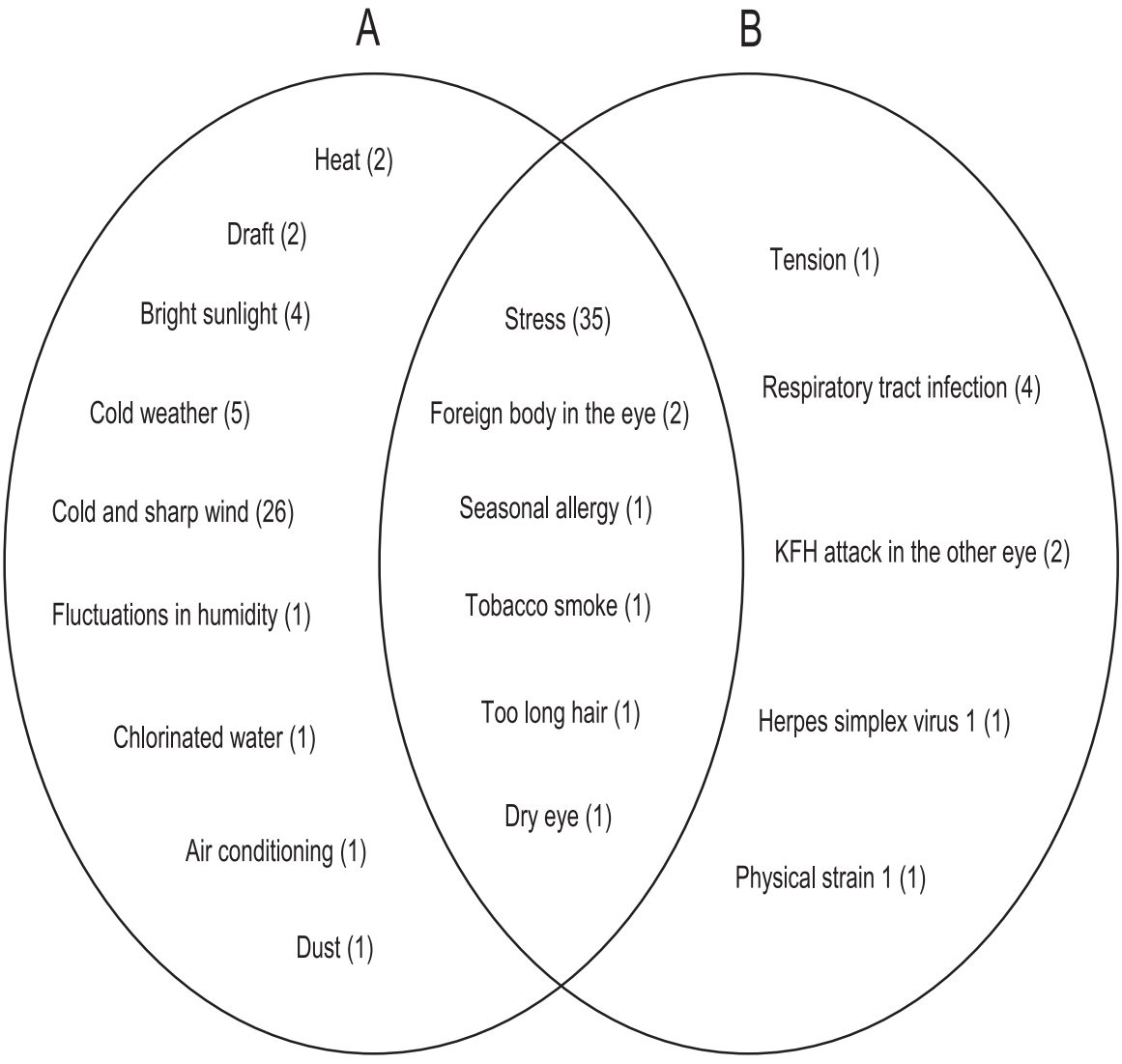


**FIGURE 3. Triggering factors predisposing to an acute attack of keratitis fugax hereditaria (KFH) reported by 60 patients. Set A includes environmental factors and set B endogenous factors. Overlapping area shows shared factors.**

cornea or central oval opacity). The remaining patients included 2 with corneal transplants and 3 with borderline mild corneal haze. When the thinnest pachymetry values of right eyes with a clear cornea (median, 504 µm; $n = 39$) were compared with those with a central oval opacity (median, 488 µm; $n = 31$), the latter had lower pachymetry values, but no difference could be confirmed between the groups (thinnest: $P = .14$; apex: $P = .26$, Mann-Whitney $U$ test) (Table 2). The thinnest points of the corneas were not located systematically in the same direction from the apex. Patients with a low BCVA and dense central corneal opacities had irregular tomography patterns.

• **TREATMENT:** Evidence-based treatment for KFH is unavailable. Various medications had been used during the acute attack (Supplemental Table 3). On the basis of the questionnaire, 33 patients (55%) had received topical steroids, 14 patients (23%) topical and 16 patients (27%) oral nonsteroidal anti-inflammatory drugs (NSAIDs), and 16 patients (27%) had not taken any medication.

Fifteen questionnaire respondents (25%) did not use any optical correction. The others wore spectacles, including 8 who additionally wore contact lenses regularly. One wore soft contact lenses, but the 7 other patients wore scleral contact lenses because of reduced BCVA and presumed higher-order aberrations. Scleral contact lenses improved BCVA 1 to 5 lines (logMAR) in all patients (Supplemental Table 4), and patients reported less distortion and blurring of vision. The number of contact lens wearers was too small to statistically confirm that scleral contact lenses improve the BCVA. Four of 7 patients reported that the number of attacks seemed to decrease after they began to wear scleral contact lenses, especially under windy conditions such as sailing.

**TABLE 2.** Pachymetry and Cylinder Power Measurements by Main Type of Corneal Opacity

| Measurement | Patients With No Corneal Opacity ($n = 39$) | Patients With Central Oval Corneal Opacity ($n = 31$) |
|---|---|---|
| Pachymetry apex | | |
| Median (IQR) | 514 (480-535) | 503 (479-520) |
| Range, μm | 373-622 | 387-597 |
| | $P = .26$, Mann-Whitney *U* test | |
| Pachymetry thinnest | | |
| Median (IQR), μm | 504 (476-530) | 488 (468-510) |
| Range, μm | 229-615 | 326-584 |
| | $P = .14$, Mann-Whitney *U* test | |
| Cylinder power | | |
| Median (IQR), D | 0.6 (0.4-1.0) | 1.0 (0.5-1.4) |
| Range, D | 0.1-1.7 | 0.3-4.6 |
| | $P = .07$, Mann-Whitney *U* test | |

Note: Measurements were performed by Fourier domain, swept-source anterior segment optical coherence tomography.

• **OCULAR COMORBIDITIES:** As indicated on the questionnaire, the most common reported diseases were dry eye (14 patients [23%]), allergic keratoconjunctivitis (11 patients [18%]), and cataracts (11 patients [18%]). Additionally, 13 patients (22%) had been diagnosed with presumed anterior uveitis and 2 patients with presumed herpes simplex keratitis. Five patients (8%) had a history of posterior vitreous detachment, 4 (7%) high intraocular pressure, 4 (7%) blepharitis, and 2 (3%) optic neuritis. Twelve patients (20%) had undergone intraocular surgery. Penetrating keratoplasty had been performed in 1 patient with corneal opacity[3] and in 1 with keratoconus, after which acute attacks and other symptoms of KFH ceased.

• **GENERAL HEALTH:** The most frequently reported systemic conditions (Table 3) were hypercholesterolemia (22%, 13/60), history of cancer (15%, 9/60), high blood pressure (12%, 7/60), and atopy (10%, 6/60). Most patients (55%, 33/60) did not smoke. Two patients (3%) were former smokers. The first 3 most common systemic conditions appeared mostly after age 40 years.

Except for headache in 24 patients (40%), other frequently reported CAPS-associated symptoms, such as urticaria, unspecific fever, arthritis, joint pain after cold exposure, abnormal sweating, frequent nausea, hearing problems, or abnormal skin pigmentation, were rare and had been experienced at least once during their lifetime by 2 to 13 patients, depending on the symptom (Table 4). The most common symptoms—headache, arthritis, and abnormal skin pigmentation—typically were associated with unrelated systemic diseases or old age.

• **QUALITY OF LIFE:** The effect of KFH on self-reported quality of life was greater if the patient had a central oval corneal opacity (Spearman $\rho = -0.57$, $P = <.001$) or decreased BCVA (Spearman $\rho = 0.45$, $P = .001$), but no correlation was found between quality of life and age of onset or current age. Responses varied widely when the respondents were asked to quantitate the impact of KFH on their quality of life (Figure 4). The median value was 5 (range, 1-10; IQR, 2-7).

## DISCUSSION

We found a wide spectrum of symptoms from KFH, ranging from patients who experienced only a few attacks during their lifetime, including 1 carrier without any symptoms, to others with severe and prolonged visual blur. Currently, there is no specific treatment for KFH, although most patients had used topical corticosteroids or NSAIDs to alleviate symptoms. The attack is clearly an inflammatory reaction, so it is logical that corticosteroids or NSAIDs have been prescribed. Because of the self-limiting nature of the attacks, almost one-third had not used any medication.

We show that rigid scleral contact lenses can improve BCVA in patients with typical central oval opacities and reduced vision from KFH. We consequently now recommend rigid, especially scleral contact lenses as the first-line treatment for reduced vision from corneal opacities and aberrations. Scleral lenses give, in addition to better visual acuity, protection to the eye surface.[10-13]

To the best of our knowledge, KFH has so far been reported only in Finland, the population of which has a high allele frequency of 0.014% for the common c.61G>C variant (rs200154873). However, until we recognized it as a surprisingly common cause of acute keratitis, typi-

**TABLE 3.** Nonocular Diseases and Disorders Reported Through a Questionnaire

| Disease | Total ($N = 60$) | Age at Diagnosis <40 Years | Age at Diagnosis ≥40 Years |
|---|---|---|---|
| Hypercholesterolemia | 13 (22) | — | 13 (22) |
| Cancer[a] | 9 (15) | 2 (3) | 7 (12) |
| High blood pressure | 7 (12) | — | 7 (12) |
| Atopy | 6 (10) | 6 (10) | — |
| Hypothyroidism | 5 (8) | — | 5 (8) |
| Mental/behavioral disorder[b] | 5 (8) | 3 (5) | 2 (3) |
| Cardiac disease | 4 (7) | — | 4 (7) |
| Migraine | 4 (7) | 4 (7) | — |
| Osteoarthritis | 4 (7) | — | 4 (7) |
| Benign prostatic hyperplasia | 2 (3) | — | 2 (3) |
| Anosmia | 2 (3) | 1 (2) | 1 (2) |
| Bronchial asthma | 2 (3) | 1 (2) | 1 (2) |
| Irritable bowel syndrome | 2 (3) | 1 (2) | 1 (2) |
| Juvenile idiopathic arthritis | 2 (3) | 2 (3) | — |
| Multiple sclerosis | 2 (3) | 1 (2) | 1 (2) |
| Psoriasis | 2 (3) | 2 (3) | — |
| Actinic keratosis | 1 (2) | — | 1 (2) |
| Castleman disease | 1 (2) | — | 1 (2) |
| Complex regional pain syndrome | 1 (2) | — | 1 (2) |
| Diffuse idiopathic skeletal hyperostosis | 1 (2) | — | 1 (2) |
| Discoid lupus erythematosus | 1 (2) | — | 1 (2) |
| Hearing loss | 1 (2) | — | 1 (2) |
| Hyperparathyroidism | 1 (2) | — | 1 (2) |
| Osteoporosis | 1 (2) | — | 1 (2) |
| Pleural emphyema | 1 (2) | — | 1 (2) |
| Polymyalgia rheumatica | 1 (2) | — | 1 (2) |
| Respiratory polyps | 1 (2) | — | 1 (2) |
| Sleep apnea | 1 (2) | — | 1 (2) |
| Acne | 1 (2) | 1 (2) | — |
| Addison disease | 1 (2) | 1 (2) | — |
| Breast and uterine inflammation | 1 (2) | 1 (2) | — |
| Dyslexia | 1 (2) | 1 (2) | — |
| Epilepsy | 1 (2) | 1 (2) | — |
| Harlequin syndrome | 1 (2) | 1 (2) | — |
| Henoch–Schönlein purpura | 1 (2) | 1 (2) | — |
| Hepatitis | 1 (2) | 1 (2) | — |
| Herpes simplex | 1 (2) | 1 (2) | — |
| Restless legs syndrome | 1 (2) | 1 (2) | — |
| Vitiligo | 1 (2) | 1 (2) | — |

Note: Data are presented as *n* (%).

[a]Breast cancer ($n = 2$), prostate cancer ($n = 2$), non-Hodgkin lymphoma ($n = 2$), squamous cell carcinoma ($n = 1$), cholangiocarcinoma ($n = 1$) and bladder cancer ($n = 1$).

[b]Anxiety disorder ($n = 1$), depression ($n = 2$), posttraumatic stress disorder ($n = 1$), and bipolar disorder ($n = 1$).

cally misdiagnosed as mild anterior uveitis, it was essentially unknown among Finnish ophthalmologists. The gnomAD database indicates the corresponding allele frequency is nearly equal (0.011%) in Sweden (Supplemental Table 1),[9] which strongly suggests that KFH currently goes unrecognized in Sweden. Further evidence is that the birthplaces of the oldest known ancestors in the families with KFH are localized to the Western and Southwestern coastal regions of Finland that historically have had close contacts with Sweden and are still mainly Swedish-speaking regions in Finland, a country that has 2 official languages, Finnish and Swedish. The gnomAD database further suggests that individual families, possibly of Nordic descent, exist outside Finland and Sweden.

The population of Finland is currently 5.54 million and that of Sweden 10.23 million; thus, according to public exome and genome databases, more than 700 and 1000 *NLRP3* c.61G>C variant carriers could live in Finland

**TABLE 4.** Cryopyrin-Associated Periodic Syndrome Symptoms Reported by Questionnaire ($N = 60$)

| Symptom | Yes | Possibly | No |
|---|---|---|---|
| Headache | 24 (40) | 2 (3) | 34 (57) |
| Arthritis | 13 (22) | 6 (10) | 41 (68) |
| Abnormal skin pigmentation | 11 (18) | 7 (12) | 42 (70) |
| Abnormal sweating | 9 (15) | 4 (7) | 47 (78) |
| Urticaria | 7 (12) | 9 (15) | 44 (73) |
| Arthralgia | 6 (10) | 8 (13) | 46 (77) |
| Hearing problem | 5 (8) | 6 (10) | 49 (82) |
| Nausea | 5 (8) | 3 (5) | 52 (87) |
| Unspecific fever | 2 (3) | 2 (3) | 56 (93) |

Note: Data are presented as *n* (%).

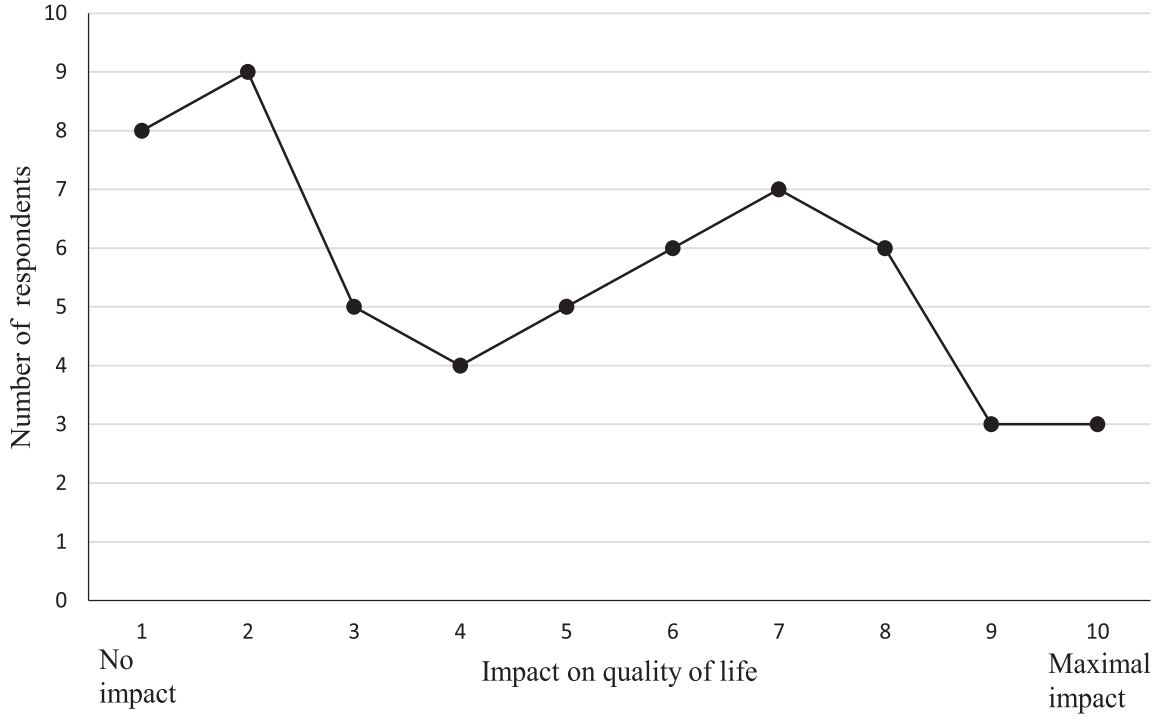


**FIGURE 4. The self-reported quality of life reported by 57 patients with keratitis fugax hereditaria (scale: 1 no impact on everyday life and 10 maximum impact).**

and Sweden, respectively. This is consistent with the ease with which we already have identified 23 families within 4 years in addition to the 2 first families reported in the 1960s and 1980s. This suggests that KFH is common in Finland because of a founder mutation that occurred more than 200 years ago in Finland or Sweden. None of our families is known to be related to the others during this time frame (Supplemental Figure). Given close historical maritime ties, suspected of facilitating the spread of rare variants[14] between Northern Poland, Sweden, Estonia, and Southern Finland, countries along the Baltic Sea other than Sweden, especially Estonia on the other side of the Gulf of Finland, also might share the c.61G>C variant. Moreover, KFH should be considered in the differential diagnosis of a patient who is an immigrant or a descendant of an immigrant from Finland or Sweden. Most emigrants from these 2 countries have moved over time to the United States and Canada, and according to the year 2019 American Community Survey, approximately 650,000 Americans reported being of Finnish ancestry and approximately 3.5 million of Swedish ancestry.[15]

Patients with KFH with or without a central corneal opacity showed pachymetry values that corresponded to the lower range of the average thickness of the normal cornea (500-575 μm),[16,17] consistent with reported thin and finely vacuolated stromal lamellae in the an-

terior half of the stroma of a patient who had undergone penetrating keratoplasty for such opacities in the past.[3] They had only mild cylinder powers. However, tomographic maps of corneas in KFH also show irregular patterns that may have higher-order aberrations that can cause starburst or glare.[18-20] Forty-seven percent of the clinically examined patients with KFH have corneal opacities and as a result, permanent irregularities that affect their refraction because of the large difference in refractive index between air and cornea.[18] Biomicroscopically visible mild stromal haze or incipient oval opacities do not yet interfere with the anterior surface, leaving BCVA unaffected.

Two-thirds of our respondents had putative factors triggering an acute attack of KFH and reported cold air, wind, and psychological stress as the most common ones. This suggests that corneal epithelial microtrauma or a systemic humoral factor might possibly trigger the acute attack. Our in vivo corneal confocal microscopy did not identify visible abnormalities in the corneal epithelium during the attack or between attacks of KFH. However, environmental factors, such as variable humidity and temperature, ultraviolet radiation, chemicals, smoking, pollutants, toxic gases, other airborne toxins, endotoxins or lipopolysaccharides, various drugs, and cosmetics, invisibly affect the homeostasis of ocular surface.[21] We hypothesize that minor stress altering the homeostasis of the corneal epithelium might activate the NLRP3 inflammasome that has been rendered hypersensitive by the pathogenic variant. This could trigger an influx of polymorphonuclear leukocytes and cause an acute autoinflammatory stromal keratitis with activation of keratocytes. Alternatively, other components of the cornea, such as its nerves, could be the cells initiating the inflammation. Further studies are needed to elucidate the molecular background of KFH.

The most common ocular comorbidities reported in KFH were dry eye disease and presumed anterior uveitis in almost one-quarter of the patients. However, KFH can easily be misdiagnosed as an exacerbation of ocular surface disease or anterior uveitis, and patients often show a mild anterior chamber reaction during their acute attack. A recent case report described KFH-like corneal findings associated with posterior scleritis in a patient with another pathogenic variant p.(R262W) in *NLRP3*, causing a systemic CASP.[22] None of our patients had experienced posterior inflammation of their eyes.

In the other 3 systemic CAPS syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous and articular syndrome), the pathogenic variants in *NLRP3* are presumed to be gain-of-function in type that enhance production of interleukin-1$\beta$.[8,23,24] Their characteristic symptoms are recurrent fever, fatigue, arthralgia, skin rash, and influenza-like muscle ache, but also chronic meningitis and sensorineural hearing loss.[4,23,24] Ocular symptoms are conjunctivitis, episcleritis, keratitis, and anterior and posterior uveitis. Elevated intracranial pressure may cause optic disk edema, followed by atrophy in neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous and articular syndrome.[25-28] Because the NLRP3 inflammasome is thought to be a body-wide machinery,[8,29] it is surprising that patients with KFH have not consistently reported any other symptoms than ocular ones.[4] Therefore, we queried them specifically for these symptoms. They did not have a convincing history of any systemic symptomatic inflammation during their attacks, although 5 or fewer individuals reported possible prodromal symptoms, such as fever, pulsating pain, or chills.

Limitations of our study include that a questionnaire introduces recall bias and one-third of the patients did not respond to it. To reduce bias, we also reviewed patient medical records for reported symptoms and comorbidities to spot any conflicting information.

The aforementioned results are from symptomatic patients, but it is possible that in the future, asymptomatic variant carriers may be found as well, in which case the results should be re-evaluated.

It is important to recognize the full clinical spectrum of KFH because it continues to be misdiagnosed as anterior uveitis or presumed herpetic keratitis. The availability of genetic testing now ensures a correct diagnosis. Research is needed in evidence-based management of acute attacks and in elucidating the molecular background of the apparent corneal specificity of autoinflammation in KFH.

*Acknowledgment*: Biostatistician Paula Bergman, University of Helsinki, provided statistical advice.

Funding/Support: The study received support from The Eye and Tissue Bank Foundation, Finland; The Eye Foundation, Finland; and Helsinki University Hospital Research Fund (TYH2019323).

Financial Disclosures: Joni A. Turunen received lecture fees from Thea Finland, Santen Finland, and Blueprint Genetics Finland, and has served on the advisory board of Novartis Finland. Minna Vesaluoma and Tero T. Kivelä received lecture fees from Santen Finland, unrelated to the present work. The other authors indicate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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