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IL6 Rs1800795 and MMP9 Rs11697325 Polymorphisms in Vocal Fold Fibroma, Laryngeal Papilloma and Chronic Hyperplastic Laryngitis: A Case–Control Study

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ABSTRACT: Background. Vocal fold fibroma and laryngeal papilloma differ in origin, yet both develop on a background of chronic mucosal inflammation and extracellular matrix remodelling. Whether inherited variation in IL6 and MMP9 contributes to these lesions, and whether such a contribution is specific to tumours or shared with chronic hyperplastic laryngitis (CHL), is unknown.

Methods. In this case–control study, 45 patients with histologically verified benign laryngeal tumours (25 fibroma, 20 papilloma), 25 patients with CHL and 30 healthy controls were genotyped for IL6 rs1800795 (–174 G>C) and MMP9 rs11697325 (–8202 A/G) by allele-specific PCR. Allelic, dominant, recessive and additive models were tested; additive models were adjusted for age and sex. A cumulative minor-allele dose (0–4) was analysed, and genotype–phenotype relations were examined in the 70 patients.

Results. All genotype distributions were in Hardy–Weinberg equilibrium. The IL6 C allele was more frequent in tumour patients than in controls (45.6% vs 25.0%; OR 2.51, 95% CI 1.23–5.14, $p=0.011$), with similar estimates for fibroma (OR 2.36) and papilloma (OR 2.71); the adjusted per-allele OR was 2.18 (1.09–4.35). The MMP9 A allele was not significantly associated with tumours (OR 1.83, 0.90–3.73) but was associated with CHL (OR 2.34, 1.05–5.20, $p=0.035$). Allele frequencies did not differ between tumours and CHL. Carrying two or more minor alleles across both loci was found in 60.0% of every patient group against 26.7% of controls (OR 4.12, 1.61–10.56, $p=0.002$). Among patients, the C-allele dose correlated with Voice Handicap Index ($q=0.30$, $p=0.011$) and the A-allele dose with the number of recurrences ($q=0.24$, $p=0.049$).

Conclusions. IL6 rs1800795 is associated with benign laryngeal tumours irrespective of histological type, while MMP9 rs11697325 shows its clearest signal in chronic hyperplastic laryngitis. The two variants appear to mark a shared susceptibility to proliferative laryngeal disease, not a tumour-specific risk. The findings are exploratory and need replication in a larger cohort.

1. INTRODUCTION

Introduction

Benign laryngeal tumours are a common cause of persistent dysphonia in adults of working age [1,2]. Vocal fold fibroma is a mesenchymal lesion of the lamina propria. Laryngeal papilloma is an epithelial lesion driven by human papillomavirus and is

known for repeated recurrence after surgery [3]. Despite these different origins, both arise in a mucosa exposed to long-standing irritation, and both involve sustained inflammation and reorganisation of the extracellular matrix.

Chronic hyperplastic laryngitis (CHL) is a diffuse, non-tumour proliferative process of the same mucosa and is regarded as a potential precursor state [4]. It therefore offers a natural comparison: a variant that predisposes specifically to tumour formation should distinguish tumours from CHL, whereas a variant that acts on inflammation or repair in general should not.

Interleukin-6 is a central mediator of chronic inflammation and epithelial proliferation. The promoter variant rs1800795 (−174 G>C) alters *IL6* transcription [5] and has been studied in many inflammatory and neoplastic conditions, including HPV-related cervical disease [6]. In the larynx the evidence is limited to squamous cell carcinoma and is inconsistent [7,8]. Matrix metalloproteinase-9 degrades type IV collagen and other matrix components. The upstream variant rs11697325 (−8202 A/G) has been associated with thoracic aortic disease [9] and with recurrent inflammatory lesions of the oral mucosa [10], but it has not been examined in laryngeal disease.

Our earlier work on vocal fold nodules, polyps and cysts examined a different *MMP9* variant (rs3918242) together with stroboscopic and histological features [11]. The present study addresses a separate question in a separate cohort: true benign tumours of the larynx and a non-tumour comparison group, analysed with formal genetic association models.

The aim was to determine whether *IL6* rs1800795 and *MMP9* rs11697325 are associated with vocal fold fibroma and laryngeal papilloma, and whether these associations differ from those seen in chronic hyperplastic laryngitis. We also tested whether the minor-allele burden relates to voice handicap, lesion extent and recurrence.

MATERIALS AND METHODS

Study design and participants

This was a single-centre case–control study with an additional disease comparison group, reported in line with STREGA recommendations [12]. One hundred unrelated adults were enrolled: 45 patients with benign laryngeal tumours (25 with vocal fold fibroma, 20 with laryngeal papilloma), 25 patients with chronic hyperplastic laryngitis, and 30 healthy controls without laryngeal disease on endoscopy. Controls came from the same region and ethnic background as the patients. The split of the tumour group into two diagnoses was specified before analysis.

Inclusion required age 18 years or older, permanent residence in the study region, written informed consent and, for patients, histological confirmation of the diagnosis. Exclusion criteria were any malignancy, severe dysplasia, acute upper airway infection at blood sampling, systemic connective tissue disease, immunosuppressive therapy in the preceding three months, and first-degree kinship with an enrolled participant.

Clinical assessment

All participants underwent ENT examination, indirect laryngoscopy and rigid or flexible laryngeal endoscopy. Duration of dysphonia was recorded in months. The number of recurrences over the preceding 24 months was recorded for patients. Voice-related disability was measured with the Voice Handicap Index (VHI) total score [13]. Lesion extent was graded endoscopically before treatment on a 0–4 scale: 0, no lesion; 1, unilateral lesion within one third of the vocal fold; 2, lesion exceeding one third or bilateral local lesions; 3, extensive glottic involvement; 4, multifocal disease beyond the glottis.

Genotyping

Peripheral venous blood (2 mL, K3-EDTA) was drawn before treatment. Genomic DNA was isolated with the DNA-Express-Blood kit (Lytech, Moscow, Russia). *IL6* rs1800795 and *MMP9* rs11697325 were typed by allele-specific PCR with SNP-Express kits (Lytech): 93 °C for 90 s; 35 cycles of 93 °C for 10 s, 64 °C for 10 s and 72 °C for 20 s; final extension at 72 °C for 60 s. Products were resolved in 3% agarose gel with ethidium bromide. Each reaction contained an internal amplification control, and each run a no-template control. Ten per cent of samples were re-typed blind with 100% concordance. The call rate was 100% at both loci.

Statistical analysis

Quantitative data are given as median [interquartile range] or mean $\pm$ SD. Groups were compared with the Kruskal–Wallis and Mann–Whitney tests; categorical data with the χ^2 test or Fisher's exact test. Hardy–Weinberg equilibrium was tested in each

group with a χ^2 test (1 df). Associations were assessed under allelic, dominant, recessive and additive models, with odds ratios (OR) and 95% confidence intervals (CI). Additive effects were estimated by logistic regression per copy of the minor allele, crude and adjusted for age and sex. A cumulative minor-allele dose (0–4) was calculated as the sum of *IL6* C and *MMP9* A alleles. Genotype–phenotype relations among patients were examined with Spearman correlation. Two-sided $p < 0.05$ was considered significant. Because two loci were tested, a Bonferroni threshold of $p < 0.025$ is also reported for the primary allelic comparisons. Analyses were performed in [software, version].

RESULTS

Participants

Sex distribution did not differ between the four groups ($\chi^2 = 1.06$, $p = 0.786$). Age differed ($H = 11.01$, $p = 0.012$): CHL patients were the oldest and papilloma patients the youngest, while the combined tumour group and controls were of similar age ($p = 0.944$). Dysphonia had lasted about twice as long in CHL as in either tumour (Table 1).

Table 1. Characteristics of the study groups

Characteristic	Controls (n=30)	Fibroma (n=25)	Papilloma (n=20)	CHL (n=25)
Age, years, mean $\pm$ SD	41.0 $\pm$ 8.5	44.0 $\pm$ 7.7	38.0 $\pm$ 9.5	47.1 $\pm$ 8.8
Men / women, n	16 / 14	16 / 9	13 / 7	16 / 9
Dysphonia duration, months, mean $\pm$ SD	—	11.4 $\pm$ 4.8	9.9 $\pm$ 4.4	25.3 $\pm$ 7.5
VHI total, mean $\pm$ SD	—	49.4 $\pm$ 13.6	55.3 $\pm$ 13.6	49.2 $\pm$ 10.0
Lesion extent score, mean $\pm$ SD	—	1.92 $\pm$ 0.64	1.95 $\pm$ 0.89	1.68 $\pm$ 0.69
≥ 1 recurrence in 24 months, n (%)	—	9 (36.0)	11 (55.0)	17 (68.0)

CHL, chronic hyperplastic laryngitis; VHI, Voice Handicap Index.

Genotype and allele distribution

Genotype frequencies at both loci conformed to Hardy–Weinberg equilibrium in every group (Table 2, Figure 1). The *IL6* C allele frequency was 0.250 in controls and 0.456 in the tumour group, with near-identical values in fibroma and papilloma. The *MMP9* A allele frequency was 0.267 in controls, 0.400 in the tumour group and highest, 0.460, in CHL.

Table 2. Genotype distribution and minor allele frequency (MAF)

Locus	Group	Major homozygote, n (%)	Heterozygote, n (%)	Minor homozygote, n (%)	MAF	HWE p
<i>IL6</i> rs1800795 (GG / GC / CC)	Controls	18 (60.0)	9 (30.0)	3 (10.0)	0.250	0.273
	Fibroma	9 (36.0)	10 (40.0)	6 (24.0)	0.440	0.346
	Papilloma	6 (30.0)	9 (45.0)	5 (25.0)	0.475	0.662
	All tumours	15 (33.3)	19 (42.2)	11 (24.4)	0.456	—
	CHL	10 (40.0)	10 (40.0)	5 (20.0)	0.400	0.405
<i>MMP9</i> rs11697325 (GG / GA / AA)	Controls	17 (56.7)	10 (33.3)	3 (10.0)	0.267	0.418
	Fibroma	9 (36.0)	11 (44.0)	5 (20.0)	0.420	0.628

Locus	Group	Major homozygote, (%)	n	Heterozygote, (%)	n	Minor homozygote, (%)	n	MAF	HWE p
	Papilloma	9 (45.0)		7 (35.0)		4 (20.0)		0.375	0.257
	All tumours	18 (40.0)		18 (40.0)		9 (20.0)		0.400	—
	CHL	8 (32.0)		11 (44.0)		6 (24.0)		0.460	0.568

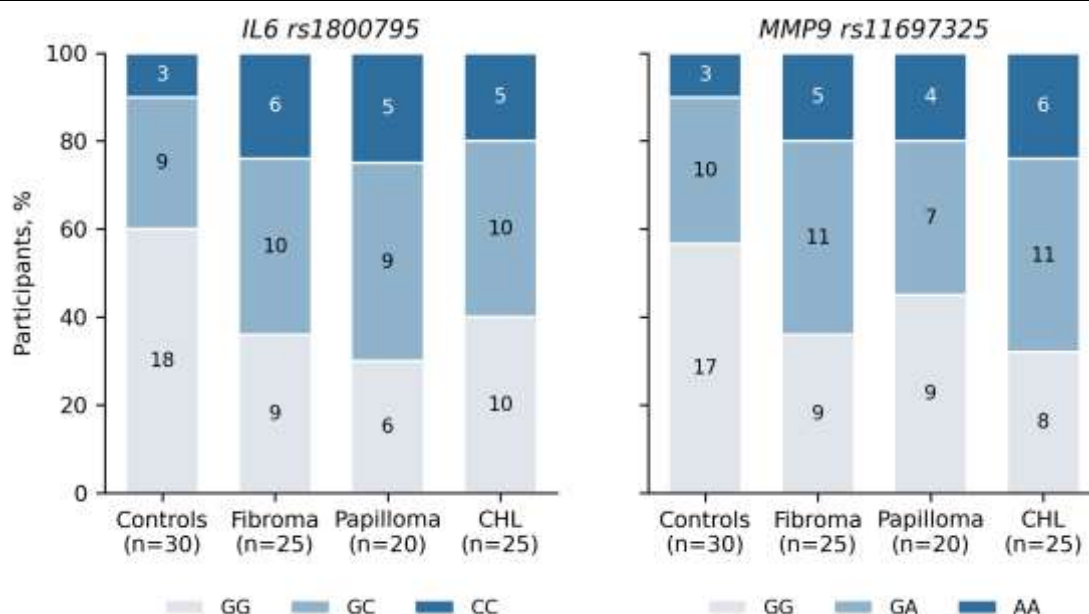


Figure 1. Genotype distribution of *IL6* rs1800795 and *MMP9* rs11697325 in the four study groups. Numbers inside the bars are participant counts. CHL, chronic hyperplastic laryngitis.

Association with disease

The *IL6* C allele was associated with benign laryngeal tumours under the allelic, dominant and additive models (Table 3, Figure 2). The allelic association remained below the Bonferroni threshold ($p=0.011$), and adjustment for age and sex barely changed the per-allele estimate (OR 2.18, 95% CI 1.09–4.35, $p=0.027$). Effect sizes were alike in the two tumour types: allelic OR 2.36 (1.05–5.29, $p=0.036$) for fibroma and 2.71 (1.16–6.37, $p=0.020$) for papilloma. In CHL the estimate pointed the same way but was not significant.

The *MMP9* A allele showed the opposite pattern. No model reached significance for the tumour group (fibroma: allelic OR 1.99, 0.89–4.44; papilloma: 1.65, 0.70–3.89). In CHL the allelic association was nominally significant ($p=0.035$), and the age- and sex-adjusted per-allele OR was 2.32 (1.01–5.33, $p=0.048$); neither passes the Bonferroni threshold. The recessive model was uninformative throughout because only three controls were minor homozygotes at each locus.

Allele frequencies did not differ between the tumour group and CHL for either locus (*IL6* C: OR 1.26, 0.62–2.53, $p=0.525$; *MMP9* A: OR 0.78, 0.39–1.57, $p=0.491$).

Table 3. Association of minor alleles with disease versus healthy controls, OR (95% CI); p

Locus	Model	All tumours (n=45)	CHL (n=25)	All patients (n=70)
<i>IL6</i> rs1800795	Allelic (C vs G)	2.51 (1.23–5.14); 0.011	2.00 (0.89–4.51); 0.093	2.32 (1.18–4.54); 0.013

Locus	Model	All tumours (n=45)	CHL (n=25)	All patients (n=70)
	Dominant (GC+CC vs GG)	3.00 (1.15–7.82); 0.023	2.25 (0.76–6.65); 0.140	2.70 (1.12–6.50); 0.025
	Recessive (CC vs GG+GC)	2.91 (0.74–11.49); 0.141	2.25 (0.48–10.53); 0.446	2.67 (0.71–9.95); 0.170
	Additive, adjusted for age and sex	2.18 (1.09–4.35); 0.027	1.85 (0.82–4.19); 0.141	2.08 (1.09–3.98); 0.026
<i>MMP9</i> rs11697325	Allelic (A vs G)	1.83 (0.90–3.73); 0.093	2.34 (1.05–5.20); 0.035	2.00 (1.03–3.89); 0.038
	Dominant (GA+AA vs GG)	1.96 (0.77–5.00); 0.156	2.78 (0.92–8.42); 0.067	2.21 (0.93–5.28); 0.071
	Recessive (AA vs GG+GA)	2.25 (0.56–9.11); 0.341	2.84 (0.63–12.80); 0.273	2.45 (0.65–9.21); 0.257
	Additive, adjusted for age and sex	1.71 (0.87–3.39); 0.122	2.32 (1.01–5.33); 0.048	1.95 (1.02–3.71); 0.043

Recessive-model p values are from Fisher's exact test.

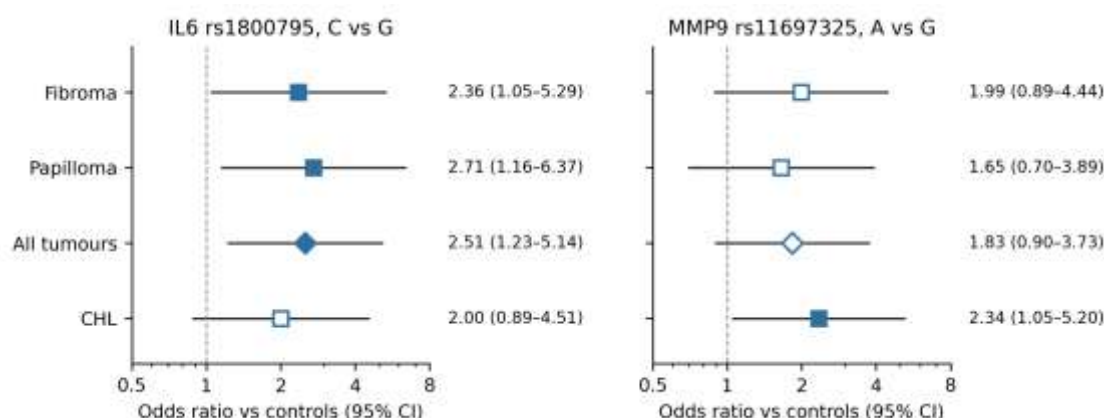


Figure 2. Allelic odds ratios with 95% confidence intervals for each patient group against healthy controls (logarithmic scale). Filled markers indicate intervals that exclude 1.

Cumulative minor-allele dose

Two or more minor alleles across the two loci were carried by exactly 60.0% of patients in each disease group and by 26.7% of controls (Table 4, Figure 3). For all patients combined this gave an OR of 4.12 (95% CI 1.61–10.56, $p=0.002$); for the tumour group alone, 4.12 (1.51–11.27, $p=0.005$). Each additional minor allele raised the age- and sex-adjusted odds of laryngeal disease about twofold (OR 2.04, 1.26–3.29, $p=0.004$). When both loci were entered in one adjusted model for all patients, each kept an independent effect (*IL6*: OR 2.13, 1.09–4.16; *MMP9*: OR 1.95, 1.02–3.74). Discrimination by the dose alone was modest (area under the ROC curve 0.69).

Table 4. Cumulative minor-allele dose by group, n

Dose	Controls (n=30)	Fibroma (n=25)	Papilloma (n=20)	CHL (n=25)
0	11	4	3	1
1	11	6	5	9

Dose	Controls (n=30)	Fibroma (n=25)	Papilloma (n=20)	CHL (n=25)
2	5	9	8	12
3	2	5	3	2
4	1	1	1	1
≥2, n (%)	8 (26.7)	15 (60.0)	12 (60.0)	15 (60.0)

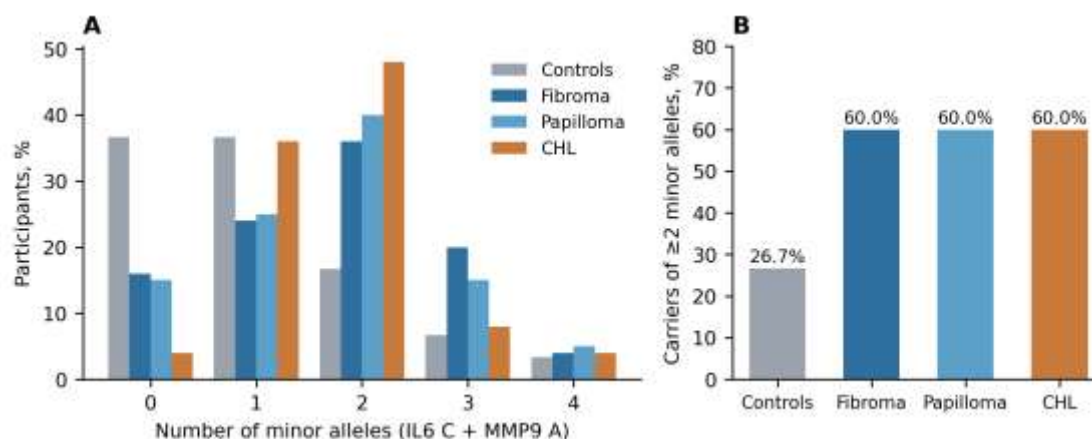


Figure 3. Cumulative minor-allele dose. (A) Distribution of the number of minor alleles across the two loci. (B) Proportion of participants carrying two or more minor alleles.

Genotype and clinical phenotype

Among the 70 patients, VHI rose with the number of *IL6* C alleles (Table 5, Figure 4A; Kruskal–Wallis $p=0.028$; $q=0.30$, $p=0.011$). C-allele carriers scored 53.9 ± 12.7 against 45.8 ± 10.6 in GG homozygotes ($p=0.008$). The C-allele dose was not related to recurrence ($q=0.05$, $p=0.692$) or lesion extent ($q=0.17$, $p=0.153$).

The *MMP9* A-allele dose correlated weakly with the number of recurrences ($q=0.24$, $p=0.049$). At least one recurrence occurred in 38.5% of GG, 58.6% of GA and 66.7% of AA patients (Figure 4B); the carrier versus non-carrier difference did not reach significance (61.4% vs 38.5%, $p=0.064$). The A-allele dose was unrelated to VHI ($q=0.10$, $p=0.409$) and lesion extent ($q=-0.05$, $p=0.682$). Neither locus correlated with age or disease duration.

Table 5. Clinical measures by genotype in patients (n=70)

Locus	Genotype	n	VHI total, mean $\pm$ SD	≥ 1 recurrence, n (%)	Extent score, mean $\pm$ SD
<i>IL6</i> rs1800795	GG	25	45.8 $\pm$ 10.6	13 (52.0)	1.68 $\pm$ 0.69
	GC	29	53.3 $\pm$ 11.2	15 (51.7)	1.90 $\pm$ 0.77
	CC	16	55.0 $\pm$ 15.4	9 (56.3)	2.00 $\pm$ 0.73
<i>MMP9</i> rs11697325	GG	26	50.9 $\pm$ 11.5	10 (38.5)	1.88 $\pm$ 0.77
	GA	29	48.5 $\pm$ 13.4	17 (58.6)	1.83 $\pm$ 0.66
	AA	15	56.1 $\pm$ 11.9	10 (66.7)	1.80 $\pm$ 0.86

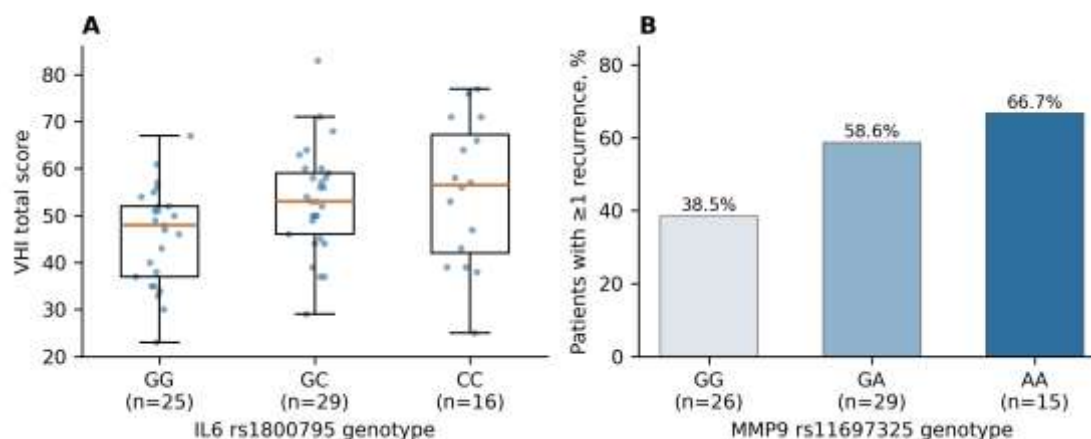


Figure 4. Clinical phenotype by genotype in patients (n=70). (A) Voice Handicap Index total score by *IL6* rs1800795 genotype; boxes show median and interquartile range, points are individual patients. (B) Proportion of patients with at least one recurrence in 24 months by *MMP9* rs11697325 genotype.

DISCUSSION

In this cohort the *IL6* rs1800795 C allele was nearly twice as frequent in patients with benign laryngeal tumours as in healthy controls, and the excess was the same whether the tumour was a fibroma or a papilloma. The *MMP9* rs11697325 A allele was not significantly associated with tumours but was most frequent in chronic hyperplastic laryngitis. Neither allele separated tumours from CHL. To our knowledge, this is the first report on rs11697325 in laryngeal disease.

We did not expect the odds ratios for fibroma (2.36) and papilloma (2.71) to be so close. One lesion is mesenchymal and the other is a virus-driven epithelial growth, so a shared genetic signal is unlikely to act through a tumour-specific pathway. We think it more likely that the C allele modifies the inflammatory response of the laryngeal mucosa to injury, whatever the trigger. This fits the regulatory nature of the variant [5] and the report linking the C allele to HPV infection and cervical neoplasia [6]. Published data on rs1800795 in laryngeal carcinoma are conflicting [7,8], and our results concern benign disease only; they do not bear on malignant risk.

The dominant model gave the largest *IL6* estimate (OR 3.00), and the additive model was also significant. This suggests that most of the excess risk appears with the first copy of the C allele. The recessive model could not be assessed reliably with three CC controls.

For *MMP9*, the direction of effect was the same in every group and every model, yet only the CHL comparison reached nominal significance. CHL patients also had the longest history of dysphonia. MMP-9 is a key enzyme of matrix turnover, and rs11697325 has been linked to recurrent aphthous stomatitis, another relapsing inflammatory mucosal condition [10], and to structural weakness of the aortic wall [9]. Against that background, an effect on slow remodelling of the laryngeal mucosa would not be surprising. The weak correlation of the A allele with the number of recurrences points the same way, but at $p=0.049$ without correction it should be read as a hypothesis, not a finding.

The absence of any difference between tumours and CHL, together with the identical 60% share of patients carrying two or more minor alleles in all three disease groups, supports the view that these variants mark a general susceptibility to proliferative change in the laryngeal mucosa. They do not indicate which form the disease will take. Both loci retained independent effects when modelled together, so their contributions appear additive.

In patients, C-allele carriers reported a greater voice handicap than GG homozygotes, by about eight VHI points. The effect is small, and VHI is a subjective measure, but the gradient across genotypes was consistent. Lesion extent did not differ by genotype, so the difference in handicap is not explained by larger lesions.

What can a clinician do with these results today? Very little. The cumulative allele dose discriminated patients from controls only modestly (AUC 0.69), which is far below what a diagnostic test requires. Genotyping may help to identify patients for closer follow-up within research protocols, but it cannot guide individual decisions.

LIMITATIONS

Our sample was small, and the subgroups of 20–25 patients even more so, so confidence intervals are wide and negative results for *MMP9* in tumours may reflect low power. Only the *IL6* allelic association passes correction for two loci. The groups differed in age, although adjustment did not change the estimates. HPV type, smoking, reflux and voice load were not included in the models. Recurrence was recorded retrospectively over 24 months. Serum or tissue IL-6 and MMP-9 levels were not measured, so no functional conclusion can be drawn. All participants came from one centre and one population, and minor allele frequencies of both variants differ between ethnic groups, so the estimates should not be transferred elsewhere without replication.

CONCLUSIONS

The *IL6* rs1800795 C allele is associated with benign laryngeal tumours, with a similar effect in vocal fold fibroma and laryngeal papilloma. The *MMP9* rs11697325 A allele shows its strongest association with chronic hyperplastic laryngitis and a weak link with recurrence. Neither variant distinguishes tumours from chronic hyperplastic laryngitis, and carrying two or more minor alleles is equally common in all three conditions. These variants are best viewed as markers of shared susceptibility to proliferative laryngeal disease. Larger multicentre studies with functional measurements are needed before any clinical use.

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Author Contributions

Gavkhar Khaydarova: Conceptualization, Methodology, Supervision, Writing—Review & Editing.

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All authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethics Statement

The study was approved by the Ethics Committee of Tashkent Medical Academy (Approval No. 387/5, dated July 10, 2026).

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to ethical approval and participant confidentiality restrictions.

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