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RESEARCH

LRIG1 levels in chronic rhinosinusitis with nasal polyps

Nazal polipe sahip kronik rinosinüzitli hastalarda LRIG1 seviyeleri

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Abstract

Purpose: Nasal polyps (NPs), usually occurring together with chronic rhinosinusitis (CRS), are benign masses of mucosal origin arising from inflammation. The transmembrane protein known as leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) is a member of the Lrig family. Lrig1 is frequently expressed in the respiratory tract and epithelial tissues and can inhibit several signaling pathways involved in cell proliferation. The aim of this study was to determine Lrig1 levels in NP tissues of patients with CRS.

Materials and Methods: This study included 36 patients with CRS and NPs and 15 patients who underwent rhinoplasty as the control group. The Lrig1 levels of all participants were measured by the ELISA method.

Results: This study revealed that Lrig1 levels were significantly lower in NP tissues than in tissues of the control group. The mean level of Lrig1 of the NP tissues was 22.2 ng/ml, while the mean level of the control group was 28.5 ng/ml. According to the results of ROC analysis, Lrig1 levels have the power to distinguish polyp tissues from control tissues (AUC=0.794). Lrig1 levels were higher in tissues with scores of 4-8 than in tissues with scores of 16-20 based on the results of computed tomography scoring. According to endoscopic evaluations, Lrig1 levels of tissues with scores of 5-8 or 9-11 were relatively lower than those of tissues with scores of 2-4.

Conclusion: Lrig1 levels were found to be decreased in NP tissues. Thus, Lrig1 may be used to confirm the presence of NPs. Lrig1 may also be helpful in NP grading. Increasing the Lrig1 levels in cases of NPs has the potential to become a targetable treatment modality.

Keywords:. Nasal polyps, Lrig1, ELISA, rhinosinusitis

Öz

Amaç: Nazal polipler (NP'ler), genellikle kronik rinosinüzit (KRS) ile birlikte ortaya çıkan, iltihaplanma sonucu oluşan mukozal kökenli iyi huylu kitlelerdir. Lösin açısından zengin tekrarlar ve immünoglobulin benzeri domainler 1 (Lrig1) olarak bilinen transmembran protein, Lrig ailesinin bir üyesidir. Lrig1 sıklıkla solunum yolu ve epitel dokularında eksprese edilir ve hücre proliferasyonunda yer alan birkaç sinyal yolunu inhibe edebilir. Bu çalışmanın amacı, KRS'li hastaların NP dokularındaki Lrig1 düzeylerini belirlemekti.

Gereç ve Yöntem: Bu çalışmaya KRS ve NP'li 36 hasta ile rinoplasti yapılan 15 hasta kontrol grubu olarak dahil edildi. Tüm katılımcıların Lrig1 seviyeleri ELISA yöntemi ile ölçüldü.

Bulgular: Bu çalışma, Lrig1 seviyelerinin NP dokularında kontrol grubuna göre önemli ölçüde düşük olduğunu ortaya koydu. NP dokularının ortalama Lrig1 seviyesi 22,2 ng/ml iken, kontrol grubunun ortalama seviyesi 28,5 ng/ml idi. ROC analizi sonuçlarına göre Lrig1 seviyeleri, polip dokularını kontrol dokularından ayırt etme gücüne sahiptir (AUC=0,794). Bilgisayarlı tomografi skorlama sonuçlarına göre Lrig1 seviyeleri 4-8 arası skorlanan dokularda 16-20 arası skorlanan dokulara göre daha yüksekti. Endoskopik değerlendirmelere göre skoru 5-8 veya 9-11 olan dokuların Lrig1 seviyeleri 2-4 skoru olan dokulara göre nispeten daha düşüktü.

Sonuç: NP dokularında Lrig1 seviyesinin düşük olduğu bulundu. Bu nedenle Lrigl, NP varlığını doğrulamak için kullanılabilir. Lrig1, NP derecelendirmesinde de faydalı olabilir. NP vakalarında Lrig1 seviyelerinin arttırılması, hedeflenebilir bir tedavi yöntemi olma potansiyeline sahiptir.

Anahtar kelimeler: Nasal polip, Lrig1, ELISA, rinosünizit

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INTRODUCTION

Nasal polyps (NPs) are a clinical condition characterized by complaints such as nasal congestion, facial pain, and loss of smell. NPs, which usually occur together with chronic rhinosinusitis (CRS), are benign masses of mucosal origin that arise from inflammation. Endoscopic evaluation and computed tomography are used to diagnose them[1]. CRS, which can be seen together with NPs, is an inflammation of the nasal cavity[2]. NPs were previously found in 18% of patients presenting with chronic sinusitis[3].

The transmembrane protein known as leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) is a member of the Lrig family and has 15 leucine-rich repeats and three immunoglobulin-like domains in its extracellular domain. Although Lrig1 is widely expressed in healthy tissues, it decreases in the presence of many cancers[4]. Lrig1 is negatively regulated by several oncogenes, including members of the ErbB family[4]. It is expressed at different levels in the respiratory tract, skin, and intestinal epithelial cells and it acts as an inhibitor of the epidermal growth factor receptor (EGFR)-dependent proliferation pathway[5-7]. Previous studies have shown the expressions and functional activities of key proteins of the ERK/MAPK pathway in cases of NPs. The overexpression of the related genes has been associated with the pathogenesis of NPs[8]. Overexpression of Lrig1 while attenuating the PI3K/AKT and Ras/Raf/ERK pathways *in vivo* and *in vitro* in cases of pituitary adenomas reversely regulated melanoma cell invasion and migration by regulating EGFR/ERK-mediated epithelial-mesenchymal transformation[9]. Lrig1 has a restrictive effect on stem cell functions[9], and genes previously expressed in stem cell studies are targets for Lrig1[9]. Cells activated by nasal damage may lead to the formation of NPs as a result of showing stem cell characteristics[10]. Studies have confirmed that the genes involved in cell proliferation are targets of Lrig1 in cases of cancer[11]. Homozygous deletion of Lrig1 causes increased expression of the ErbB receptor and highly penetrant duodenal adenomas[12].

The efficacy of the EGFR signaling pathway in nasal damage has been reported[13]. This pathway also constitutes a target for Lrig1[9]. The hypothesis of the present study is that Lrig1 levels are decreased in NP tissues relative to control tissues. Demonstration of the potential presence of the Lrig1 protein in NPs is very important for elucidating the molecular dysregulation underlying NP pathology. In the present study, we investigate Lrig1 protein levels in patients with CRS and NPs. We show for the first time that levels of Lrig1 protein are decreased in NP tissues relative to control tissues. The presence of the Lrig1 protein and the possible relationship of this protein's expression with clinical data in cases of CRS and NPs may support the discovery of drugs that may be developed to treat these diseases. In this study, Lrig1 levels were measured by ELISA method in tissues obtained from 36 patients with NPs.

MATERIAL AND METHODS

Subjects

Patients (n=36) with CRS and NPs who underwent surgery for nasal polyposis in the Otorhinolaryngology Department of the Ataturk University Faculty of Medicine between 2020 and 2022 were prospectively included in this study. Control tissues were obtained from 15 patients who underwent rhinoplasty. The tissues required for the study were collected by specialist doctor Abdulkadir Şahin from the Otorhinolaryngology Department of the Faculty of Medicine of Ataturk University. The preservation of the tissues and the experimental protocol were carried out by Sevgi Karabulut Uzunçakmak, Ayşegül Tavacı Özçelik, and Zekai Halıcı in the Medical Pharmacology Laboratory of Ataturk University. The study was approved by Ataturk University's Clinical Research Ethics Committee (date and number: 26.03.2020, 03/29) and was carried out in accordance with the ethical standards of the 1975 Declaration of Helsinki as revised in 2000. Patients were diagnosed with CRS and NPs according to the diagnostic criteria of the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps[14]. All patients were informed about the study and provided written informed consent. Clinical and demographic information was accessed from hospital records. Although approximately 50 patients were considered for inclusion, only 36 were enrolled in the study after patient histories were reviewed and the exclusion criteria (autoimmune diseases, known immunodeficiency syndromes, and cystic fibrosis) were applied. The samples of polyp tissues and control tissues were obtained during surgeries.

Nasal endoscopic evaluation

Nasal endoscopic evaluations were performed with a 0-degree 4-mm rigid endoscope (Karl Storz, Germany). The inferior turbinate, middle turbinate, middle meatus, nasal cavity, and nasal mucosa were evaluated. The Lund-Kennedy (LK) system was used for staging[15]. In this system, grade 0 entails no polyps, grade 1 entails polyps limited to the middle meatus, and grade 2 entails polyps overflowing from the middle meatus. The presence of discharge is scored as follows: 0 = no discharge, 1 = clear and thin discharge, 2 = purulent and thick discharge. The presence of mucosal edema, scarring, and crusting is scored as follows: 0 = absent, 1 = mild, 2 = severe. Scores were calculated separately for each nasal cavity and the sum was recorded.

Sinus computed tomography (CT) evaluation

In CT examinations of the sinuses, the coronal, sagittal, and axial planes were used. The Lund-Makkay (LM) system was used for staging[16] and scores were recorded for the maxillary sinus, anterior ethmoid sinus, posterior ethmoid sinus, frontal sinus, sphenoid sinus, and ostiomeatal complex. All sinuses received 0 points if there was no opacification, 1 point if there was partial opacification, and 2 points if there was complete opacification. For the ostiomeatal complex, a score of 0 was given if there was no obstruction and a score of 2 was given if obstruction was present. The score for each side was calculated separately and then the total was recorded.

Enzyme-linked immunosorbent assay (ELISA)

Samples of polyp tissues and healthy tissues (100 mg) were homogenized with 0.1 M phosphate-buffered saline (pH 7.4) using a TissueLyser II device (QIAGEN, Germany). The homogenates were centrifuged at 5000×g and 4°C for 5 min. The supernatants were then separated into new tubes and stored at -80°C until analysis. Lrig1 levels in the tissues were measured using a commercial kit (Bioassay Technology Laboratory, China) according to the manufacturer's instructions by sandwich ELISA method.

Statistical analysis

Data analysis was performed using GraphPad Prism 5.0 (GraphPad Software, USA). The normality of the data was evaluated by Shapiro-Wilk test. Differences between two groups were analyzed by Mann-Whitney *U* test. In cases of more than two groups, the Kruskal-Wallis test was used to examine the differences. The Dunn test was used as a post hoc test. Receiver operating characteristic (ROC) curve analysis was used to discriminate between the Lrig1 levels of polyp tissues and healthy tissues. Values of $p<0.05$ were considered significant.

RESULTS

This study included 36 patients with a mean age of 45.4±16.04 years. While 42% (n=15) of these patients were women, 58% (n=21) were men. Only one of the patients was a smoker. Six of the patients had a history of asthma. Thirty-two patients underwent polypectomy for the first time and 4 patients underwent revision surgery. Panpolyposis was seen in 24 cases; among the other patients, antrochoanal polyps, bilateral ethmoidal polyps, and one-sided polyps were observed. The mean age of the rhinoplasty patients was 39±14.2 years, and 10 of these patients were women while 5 were men.

The LRIG1 levels of polyp and control tissues were measured by ELISA. Lrig1 levels were significantly lower in NP tissues compared to control tissues (p=0.0004) (Figure 1).

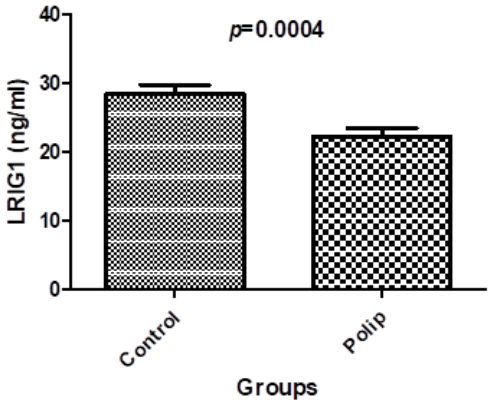

Figure 1. LRIG1 levels in the polyp tissues and control tissues.

ROC curve analysis was performed for Lrig1 levels to discriminate NP tissues from control tissues. The

area under the curve (AUC) and p-values for NPs are shown in Figure 2. The cut-off point for the Lrig1 levels of NPs was <24.67 ng/mL with 0.806 sensitivity (95% CI: 0.6253-0.9255) and 0.714 specificity (95% CI: 0.4782-0.8872) to discriminate NP tissues from control tissues.

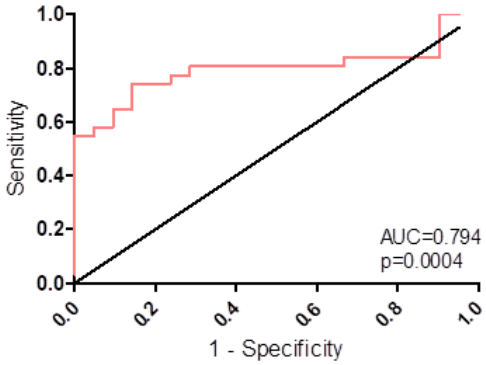

Figure 2. ROC curve analysis for LRIG1 to discriminate nasal polyp tissue and control tissues

The NPs of the patients were staged according to CT findings. We grouped the tissue samples according to CT scores of 4-8, 9-15, and 16-20 (Figure 3). When we compared Lrig1 levels according to these groups, we observed a significant difference among the groups (p=0.0104). The Lrig1 levels were higher in the group with the lowest CT scores (4-8) and lower in the group with the highest CT scores (16-20).

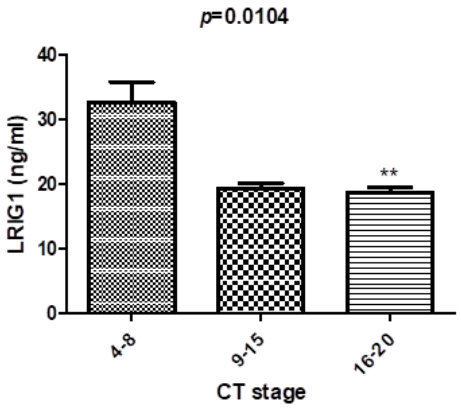

Figure 3. LRIG1 level according to tomographic staging. ** according to group (4-8)

Lrig1 levels were also analyzed in NP tissues according to endoscopic scoring and were found to be decreased in tissues with higher endoscopic scores (p=0.0011). As shown in Figure 4, the levels of Lrig1 in tissues with endoscopy scores of 2-4 were relatively higher than those of tissues with endoscopic scores of 5-8 and 9-11.

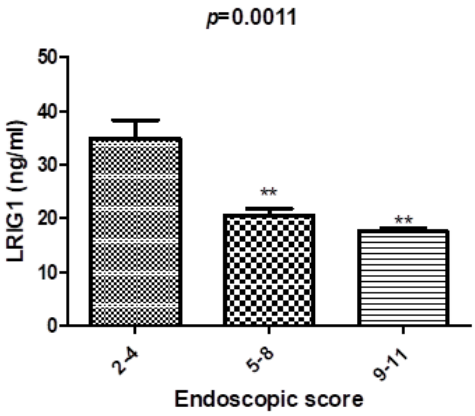

Figure 4. LRIG1 level according to endoscobic scoring. ** according to group (2-4).

DISCUSSION

The human nasal epithelium constantly repairs itself to maintain its integrity against irritating agents in the environment. Damaged areas are repaired by the underlying basal cells. Disruption of the epithelial repair mechanism in damaged areas may cause chronic inflammation of the nasal mucosa. Inflammatory cells, mucosal inflammation, and epithelial remodeling are all characteristic of NPs. In the presence of extracellular matrix deposition and submucosal edema, NPs grow with the interactions of stromal, epithelial, and inflammatory cells[17]. These tissue growths originate from the ethmoid sinus, do not turn into cancer, and should not cause pain[18].

Lrig1 is a tumor suppressor protein that acts via the RTK-RAS-RAF signaling pathway[19]. Lrig1 can diminish the effects of PI3K/AKT and Ras/Raf/ERK pathway signaling, as well as negatively regulating the EGFR-ERK pathway and thus limiting epithelial-mesenchymal transformation[9]. Lrig1 is frequently expressed in the respiratory tract and epithelial tissues and it can

inhibit EGFR-mediated signaling pathways[5-7]. Lrig1 restricts cell proliferation and suppresses the functions of genes that mediate cell proliferation. Decreased Lrig1 expression causes increased phosphorylation of EGFR, RTK, and insulin receptors[19], and the ERK-MAPK pathway is involved in NP pathogenesis[8]. Recombinant Lrig1 can suppress the proliferation of melanoma cells by inhibiting the PI3K-AKT pathway, which shows RTK-dependent activity[19].

Increased ErbB4 expression was previously demonstrated for NPs compared to control samples[20]. Epithelial cells activated by nasal damage contribute to the formation of NPs by assuming stem cell characteristics[10]. NP tissues can also transform into other normal mesenchymal-derived stem cells as a result of the mesenchymal stem cells that they contain[10,21]. ErbB activation is an important signal for stem cell proliferation[22]. Wong et al. demonstrated that ErbB signaling is a strong inducer of stem cell proliferation and that Lrig1 regulates stem cell activities by limiting the extent of ErbB signaling in the intestinal stem cell niche[22].

The EGFR signaling system plays an active role in cell proliferation and differentiation[20,23]. EGFR is expressed in epithelial cells of the respiratory pathway and increased EGFR expression has been previously reported in cases of bronchial asthma and CRS with NPs[24,25]. EGFR plays an active role in repairing epithelial damage. At the same time, it interacts with many different genes and ensures epithelial repair and remodeling[13,26]. Duan et al. showed that EGFR expression was relatively strong in the nasal epithelium in cases of basal cell hyperplasia compared to healthy epithelium based on their staining of NP tissues and healthy epithelial tissues[20]. They also showed increased EGFR expression in NP tissues[20]. Shimizu et al. suggested that EGFR inhibitors may be therapeutic targets in the treatment of intractable cases of eosinophilic inflammation seen with bronchial asthma and nasal polyposis[27]. Lrig1 negatively regulates EGFR and EGFR-related genes[28].

ERK accelerates cell proliferation in NP tissues[29]. The phosphorylation of MEK1/2 and ERK1/2 was detected at relatively higher levels in NP tissues compared to healthy control tissues[8]. Cheng et al. reported higher levels of p-Akt and PI3K protein expression in NP tissues obtained from patients with both NPs and CRS compared to control tissues. They suggested that the PI3K/Akt pathway may be involved in the pathogenesis of CRS and NPs, and it may be used as a therapeutic target for the treatment of many diseases[30]. Diminished Lrig1 expression via RNA interference may lead to incorrect responses to glioma cells via EGFR and protein kinase B (AKT) activation[31]. In a study conducted by Zhang et al., Lrig1 expression was found to inhibit the hypoxia-induced EGFR/PI3K/AKT pathway in SHG-44 cells[32]. The downregulation of Lrig1 in hypoxic conditions is also dependent on HIF-1α[33]. HIF-1α is involved in the generation of epithelial-mesenchymal transitions and hypoxic conditions in the nasal epithelium. In a previous murine model of NPs, HIF-1α inhibitors were shown to suppress the occurrence of polypoid lesions[34].

This study is the first study to date that presents an evaluation of Lrig1 levels in NP tissues. Our discussion here has been based on Lrig1-related genes. In our study, Lrig1 was found to be significantly decreased in NP tissues relative to control tissues and, according to the results of ROC analysis, Lrig1 levels have the power to distinguish between NP tissues and healthy tissues. At the same time, decreased Lrig1 levels are predictive of increased CT scores. In light of our findings and those of the previous studies reported here, it may be concluded that Lrig1 may have effects on the suppression of stem cell properties, the restriction of cell proliferation, and negative regulation of RTK and ErbB signaling. Cell proliferation increases during nasal tissue repair with deterioration in the balance of epithelial cells and stem cells, and such cellular alterations also trigger changes in signaling pathways and result in changes in gene expressions. We suggest that the increased gene expression levels related to cell proliferation may cause a decrease in the Lrig1 level. In the other direction, it is possible that decreased Lrig1 levels in cases of NPs may cause increased proliferation and increased expression of stem cell genes.

The present study has several limitations. Due to the exclusion criteria, it was difficult to enroll the targeted number of patients in the study. We also encountered obstacles in accessing all patients' full clinical data. Another limitation was the inability to study the expression of Lrig1-related genes.

With this study, we offer new findings to confirm the expression of previously studied genes in NP tissues. Lrig1 may be used to differentiate between polyp tissues and healthy tissues. The increased expression levels of Lrig1 in cases of NPs may inspire

researchers to pursue new treatment goals in this area. Research carried out on this topic with larger patient populations and more Lrig1-related genes would contribute to our understanding of the changing molecular mechanisms involved in cases of NPs.

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