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# UNRAVELLING THE GENETIC ETIOLOGY OF NON-SYNDROMIC HEREDITARY GINGIVAL FIBROMATOSIS: A LITERATURE REVIEW AND CASE REPORT

Dental Science

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## ABSTRACT

Hereditary gingival fibromatosis is a rare condition that affects the gingiva and is characterized by a benign, fibrous overgrowth that can occur alone or as part of a syndrome. Clinically, it is associated with a pink gingiva with distinct stippling that covers nearly the entire tooth surface, frequently preventing their eruption. It is frequently reported during the transition from primary to permanent dentition, which left untreated may have a negative psychological impact at that age. The aim of this review is to provide a clinical insight, as well as a summary and discussion of the role of potential genes, chromosomal regions, and genetic variations in the pathogenesis of this rare disease. In addition, this paper describes a family with a non-syndromic form of hereditary gingival fibromatosis exhibiting significant clinical variability, ranging from severe generalized gingival overgrowth in a 19-year-old boy, to minimal manifestations in his maternal grandmother. The treatment modality used to treat this patient and measures taken to prevent the recurrence of this condition have also been discussed in detail.

## KEYWORDS

Hereditary gingival fibromatosis, gingivectomy, internal bevel incision, external bevel incision, gingival overgrowth.

## INTRODUCTION

Hereditary gingival fibromatosis (HGF) is a rare disease that has a prevalence of 1 in 750,000 individuals.[1] According to recent classification by 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, HGF is included in non-dental biofilm induced gingival diseases.[2]

This benign, non-inflammatory condition is characterized by gradual enlargement of gingiva over time that can be localised, generalised, diffuse, or nodular and is typically accompanied by the eruption of permanent teeth. Clinically, a pink gingiva with marked stippling can be seen to cover almost all of the tooth surface, preventing eruption in many cases. The firm and painless gingival overgrowth in these patients does not affect the alveolar bone in most of the cases, but may lead to development of psuedopockets which enhance plaque accumulation and inflammatory changes in gingival tissue may lead to periodontal destruction if left untreated. As it does not resolve spontaneously, the treatment of choice is gingivectomy which can be performed using various techniques.

HGF can be presented as an isolated entity (non-syndromic) or it can be associated with various genetic syndromes. HGF is a type of isolated gingival fibromatosis that runs in families. Pedigree analyses of affected families support a simple Mendelian transmission pattern. The majority of HGF cases appear to be autosomal-dominant, though autosomal-recessive inheritance has also been reported.[3]

Excess accumulation of extracellular matrix (ECM) components appears to contribute to the pathologic manifestation of HGF, but the molecular mechanisms underlying this remain unknown. The risk of recurrence and the lack of non-invasive therapies in dental practice to treat this condition, highlights the need for novel alternative therapies. The purpose of this article is to provide an updated review clinical features, genetic etiology, and differential diagnosis of HGF. This paper also describes a case where HGF was successfully treated and its recurrence prevented by providing a specialised pressure appliance therapy to patient.

## CASE PRESENTATION

A 19 year old male patient reported to the Department of Periodontics, Maulana Azad Institute of Dental Sciences with a chief complaint of gum swelling which he started noticing after eruption of his permanent teeth. The swelling slowly progressed involving the gingiva in both the arches and attained the current size. Masticatory problems and esthetic concerns made the patient report for treatment. The patient was thoroughly questioned regarding his physical and mental status to rule out any syndromes associated with the enlargement. His medical history was noncontributory. Detailed family history revealed presence of similar condition in his younger twin sisters aged 10 years (Figure1), his mother, maternal uncle and maternal grandmother.

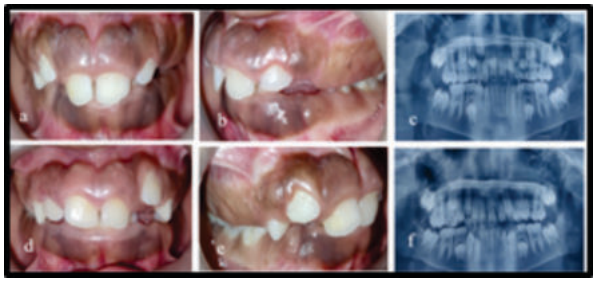

**Figure 1:** Intraoral photographs and OPG: (a, b, c) Twin sister 1 and (d, e, f) Twin sister 2

Each family member had different clinical presentation ranging from moderate to severe gingival enlargement. Pedigree analyses revealed autosomal dominant type of inheritance pattern (Figure 2).

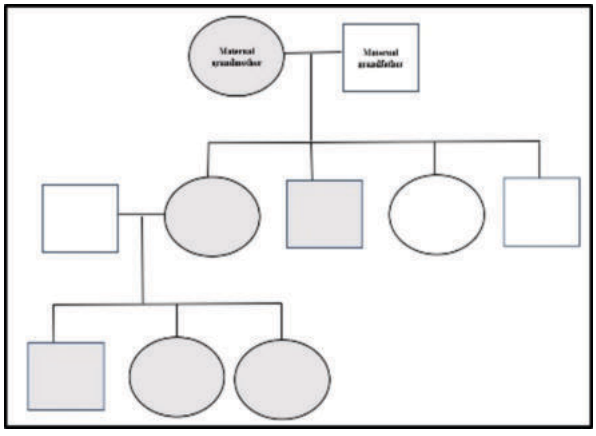

**Figure 2:** Pedigree chart showing the pattern of inheritance of HGF in the patient's family

Intra oral examination of patient revealed generalized, nodular pattern of gingival enlargement covering two third of crown structure of most of the teeth with a firm to fibrotic consistency (Figure 3a, b, c, d). Periodontal assessment revealed generalized psuedopockets and moderate calculus deposits with bleeding on probing in certain areas. OPG revealed mild horizontal bone loss in right lateral incisor and canine (tooth number # 12 and #13) (Figure 3e).

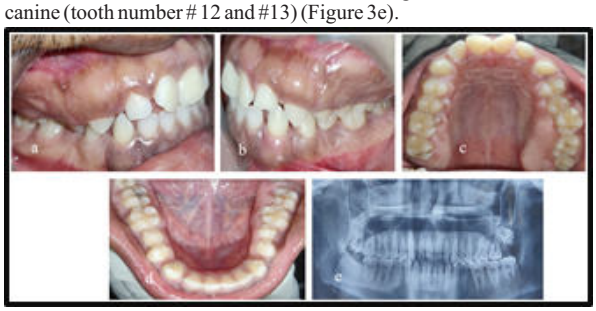

**Figure 3:** Preoperative intraoral photographs: lateral view (a, b), preoperative mirror image of upper and lower arch (c, d) and OPG (e)

To address these conditions, quadrant wise external bevel gingivectomy was proposed to the patient and surgical procedure was performed under aseptic conditions (Figure 4).

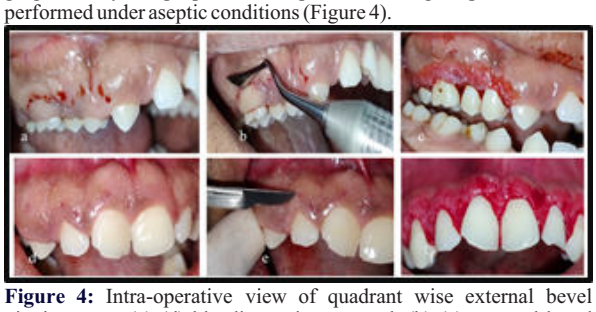

**Figure 4:** Intra-operative view of quadrant wise external bevel gingivectomy (a) (d) bleeding points created, (b) (e) external bevel incision given, (c) (f) immediate post operative view

Gross specimen of gingival tissue measuring 4.2 × 1.2 × 1 cm was send for histopathological examination. Intraoral positive pressure appliance was given to the patient after fifteen days of completion of surgery to prevent the recurrence of condition (Figure 5). The postoperative course was uncomplicated and there was no recurrence of growth up to two years of follow-up (Figure 5).

The microscopic findings were evaluated and were found to be consistent with hereditary gingival fibromatosis (Figure 6).[4]

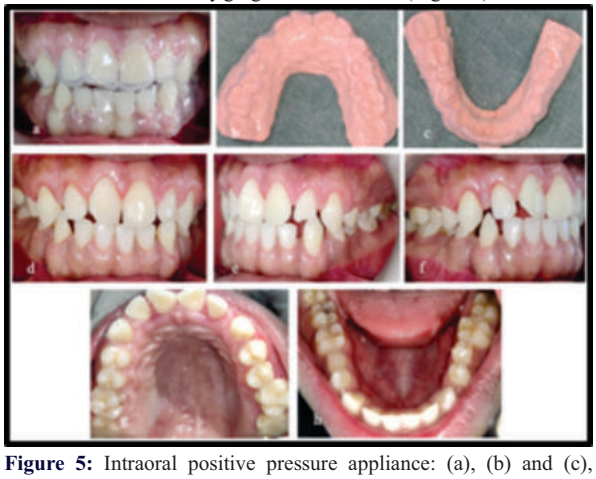

**Figure 5:** Intraoral positive pressure appliance: (a), (b) and (c), Intraoral view two year after surgery (d) frontal, (e) (f) lateral view, (g) (h) mirror images of upper and lower arches

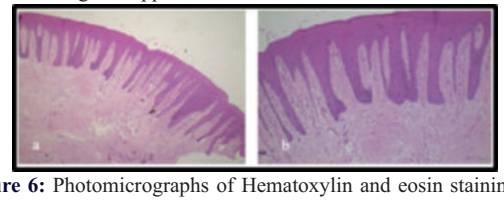

**Figure 6:** Photomicrographs of Hematoxylin and eosin staining (a) Hyperplastic epithelium with long rete pegs (b) Increased amount of collagen fiber bundles running in all directions with spindle shaped fibroblasts.

## DISCUSSION AND REVIEW OF LITERATURE

HGF is a genetically heterogeneous condition with clinical presentation of gingival overgrowth characterized by a benign, slowly progressive, non-hemorrhagic, fibrous enlargement of keratinized gingiva of maxillary and mandibular region.

Although HGF most commonly presents as an isolated clinical finding, it is found to be associated with syndromes like Laband, Rutherfurd, Jones, Cross, prune belly and Ramon syndrome.[1] Hypertrichosis, mental retardation, hearing loss, and epilepsy have most commonly been associated with this disease.[5] In addition to Mendelian and syndromic forms, gingival fibromatosis is also known to be induced by certain classes of pharmacological drugs, including phenytoin, calcium channel blockers, and cyclosporin.[6] These drugs are used in the treatment of seizure disorders (phenytoin), hypertension and angina (calcium-channel blockers), and organ transplants and autoimmune diseases (cyclosporin).

HGF is a genetically heterogenous disorder which have been proven by various linkage analysis studies done over past decades indicating the presence of disease-related genes on several chromosomal regions. According to literature, five distinct loci related to the non-syndromic variant of HGF have been identified, two on chromosome 2, one mapped to chromosome 5, one to chromosome 11, and one to chromosome 4.[7-11] A novel heterozygous missense mutation in zinc finger protein 862 gene (ZNF862) is recently identified and is proposed to be responsible for increasing the profibrotic factors particularly COL1A1 synthesis and hence resulting in HGF.[12]

Whole-exome sequencing (WES) and bioinformatics analyses have identified ALK receptor tyrosine kinase gene (ALK) (c.361C > T) and collagen type I receptor and thrombospondin receptor gene (CD36) (c.1133G > T) as newer genes that cause HGF.[13]

Hence till date, various chromosomal region (2p21-p22, 2p22.3-p23.3, 4q12, 5q13-q22, and 11p15) and affected genes such as REST (RE1-silencing transcription factor), SOS1 (Son-of-Sevenless-1), ZNF862 (zinc finger protein 862 gene), ALK receptor tyrosine kinase gene (ALK) (c.361C > T) and collagen type I receptor and thrombospondin receptor gene (CD36) (c.1133G > T) have been identified to be associated with non-syndromic form of HGF (Table 1).

**Table 1: Affected Gene And Chromosomal Region Contributing To Non-syndromic HGF**

| Chromosomal region/ gene locus | Affected gene | Inheritance pattern | References |
|---|---|---|---|
| 2p21-p22 GINGF, GINGF1, GGF1 | SOS-1 | Autosomal dominant | TC Hart et. al 1998 |
| 5q13-q22 GINGF2, GGF2 | CAMK4 | Autosomal dominant | Xiao et. al 2001 |
| 2p22.3-p23.3 GINGF3, GGF3 | unknown | Autosomal dominant | Ye et. al 2005 |
| 11p15 GINGF4, GGF4 | unknown | Maternal inheritance | Zhu et. al 2007 |
| 4q12 GINGF5, GGF5 | REST | Autosomal dominant | Bayram et. al 2017 |
| 7q36.1 | ZNF862 | Autosomal dominant | Wu et. al 2022 |
| 2p23.2–p23.1 | ALK | Autosomal dominant | Machado et. al 2023 |
| 7q11. 2 | CD36 | Autosomal dominant | Machado et. al 2023 |

Histological characteristics suggest that the expansion of gingival tissue in HGF results mostly from increased extracellular matrix (ECM) accumulation due to genetic mutation affecting intracellular signaling pathways. In addition, increased proliferation of the epithelial cells may account for the formation of elongated rete ridges. A model describing the possible pathogenesis of HGF is shown in Figure 7.[14]

HGF is likely to recur, with an overall recurrence rate of **34.92%** after surgical treatment. The recurrence rate is related to age, surgical technique and operation, location of hyperplasia, and genetics.[14]

Recurrence is generally considered to be minimal if the surgery is performed after eruption of the permanent dentition. There are many reported cases in the literature showed no recurrence in a period of 2 years, 3 years, or even 14 yearsof follow up.[15]

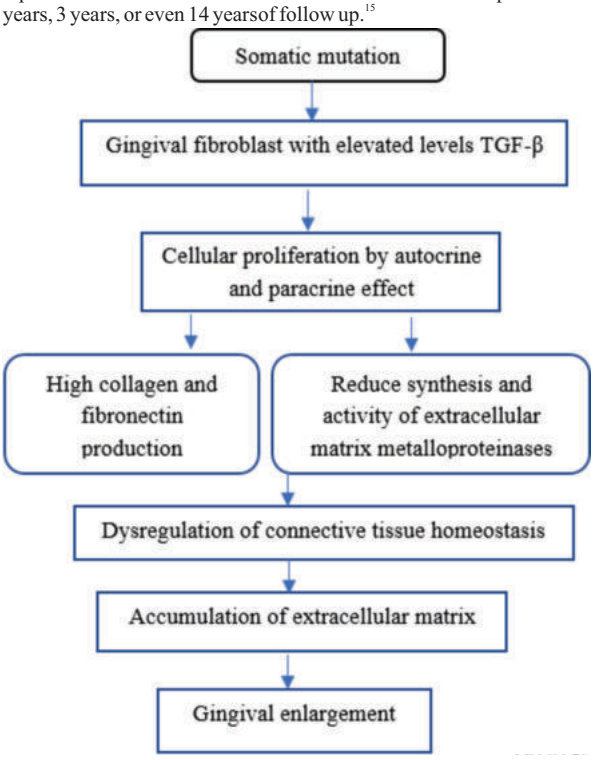


**Figure 7: A pathogenesis model for HGF-related gingival hyperplasia:** Gingival fibroblasts produce more TGF- β as a result of somatic mutations, which promotes cellular proliferation, excessive collagen and fibronectin production, and decreased activity of metalloproteinases that break down the extracellular matrix. Due to the dysregulated connective tissue homeostasis, extracellular matrix builds up and results in gingival enlargement.

To prevent the recurrence in the present case, a special positive pressure appliance was given to the patient two weeks postoperatively and was instructed to be worn at night.[16] Two years follow up exhibited no postoperative complications or recurrence. Patient's younger twin sisters were kept on follow up and were planned for definitive treatment once all the permanent teeth are erupted into the oral cavity.

## CONCLUSION

HGF is a disorder exhibiting high genetic heterogenicity. With advancement in research and numerous genomic studies being done by different investigators, a greater number of genes responsible for this condition might be identified in future.

Early diagnosis and treatment are important to prevent it from progressing to more severe periodontal problems. To prevent recurrence, positive pressure appliance therapy may be considered along with regular follow up and patient motivation regarding oral hygiene maintenance.

**Conflict Of Interest:** The authors state that they do not have any conflicts of interest.

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