Localized Juvenile Spongiotic Gingival Hyperplasia: Clinicopathologic and Microbiologic Correlations

Thesis

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By

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Abstract

Introduction: Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a persistent inflammatory lesion of unknown cause that primarily affects children and young adults. Usually, it involves the maxillary, anterior attached gingiva, and presents as a localized, erythematous, velvety to pebbly plaque that bleeds easily and is nontender. Furthermore, it is refractory to oral hygiene measures. Proposed causes include ectopic junctional epithelium, minor trauma, orthodontic treatment, and tooth eruption. Purpose: The purpose of this prospective investigation was twofold: 1) to identify clinical factors that may be associated with LJSGH and 2) to determine if differences exist between the bacterial profiles of a LJSGH lesion and a classic plaque-induced gingivitis lesion.

Methods: Study subjects completed a questionnaire and participated in a clinical examination that included gingival crevicular fluid sampling of both LJSGH and plaque-induced lesions. Descriptive statistics were used to analyze the clinical findings and questionnaire results. The Wilcoxon Signed Rank Sum Test was used to determine if there was a significant difference in plaque scores of teeth with LJSGH and teeth with plaque-induced gingivitis. Gingival crevicular fluid samples were sequenced and analyzed using Bray-Curtis multidimensional scaling and PERMANOVA at the Griffen-Leys Laboratory at The Ohio State University College of Dentistry.

Results: Twenty-three patients were recruited to participate in this study; only ten patients met the inclusion criteria and enrolled. 60% of LJSGH lesions occurred in females, and the mean
age of individuals was 12.5 ± 2.76. 80% of the study participants identified as Hispanic or Latino. 60% reported frequent consumption of popcorn, a food suspected of causing irritation to the gingiva. 70% of patients demonstrated lip incompetence upon clinical exam. There was no significant difference in plaque scores of teeth associated with LJSGH and those associated with plaque-induced gingivitis (α = 0.05). 60% of LJSGH-associated teeth had a dental defect. 100% of the lesions were biopsied and had a confirmatory histological diagnosis of LJSGH. Bacterial DNA analysis revealed no significant difference between the microbial communities of LJSGH sites and plaque-induced gingivitis sites (α = 0.05). **Conclusions:** The findings from this study support the current literature on LJSGH. It develops preferentially in the maxillary anterior sextant, and is associated with gingival bleeding. The subgingival bacterial communities of LJSGH lesions are not significantly different from those of classic plaque-induced gingivitis lesions. Further research is necessary to demonstrate a statistically significant relationship between LJSGH and Hispanic predominance, lip incompetence, dental defects, and trauma from food.
Dedication

This document is dedicated to my family.
Acknowledgments

I would like to acknowledge my thesis committee for their mentorship and guidance throughout this project. Without your invaluable support, this research would not have been possible. I would also like to thank Dr. Tanya Mathews, the amazing individuals at the Griffen-Leys laboratory, my co-residents, Dawn Perotta, and Dr. Jennifer Moreland for their time and effort in assisting with this project.
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Major Field: Dentistry
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Chapter 1: Introduction

Gingival diseases in the pediatric population encompass a wide range of entities with overlapping clinical manifestations. The prognosis and implications of these diseases on an individual’s oral health depend, in part, on factors such as etiology, health of the individual, location, size and extension into the surrounding hard and soft tissues and patient compliance with treatment recommendations. Gingival and periodontal health in children may be overlooked due to the limited time that primary teeth are present in the mouth, and the transitory nature of the mixed dentition. However, signs of periodontal disease in adults begin earlier in life [1]. Consequently, timely diagnosis of disease allows for the greatest opportunity for successful treatment.

The appearance of healthy gingivae can vary from individual to individual, and also depends on the location in the mouth. In general, the width of attached gingiva is greatest in the incisor and molar areas, and the least in the canine areas; it is narrower in the mandible than it is in the maxilla [1, 2]. As a child grows older, the attached gingiva and keratinized gingiva increase in width [1-3]. Healthy gingivae are often coral pink (with ethnicity accounting for some variations in color), firm, stippled, and do not bleed when probed [4]. In contrast, diseased or inflamed gingival tissues may appear erythematous, edematous, and bleed easily or spontaneously [5]. It is also important to note that the periodontium in children differ from that of adults [1]. For example, gingiva
of children tend to be more erythematous in color, lack stippling, have gingival margins that are more rounded and rolled, and have decreased sulcular depths [1].

Dental Eruption and Gingival Changes

The eruption of the permanent dentition is associated with changes in the gingival tissues [1]. Before the crown of the permanent tooth erupts into the mouth, the gingiva appears as a firm bulge that is slightly blanched, and may adapt to the shape of the unerupted crown [1]. As the permanent tooth crown erupts through the gingiva, the marginal gingiva and sulcus start to form [1]. During this stage, the gingival margin can be edematous, rounded, and slightly erythematous [1]. As a result of an initially weak periodontal attachment and temporary inflammation, the gingival sulcus of a partially erupted permanent tooth can be deeper than its primary tooth counterpart [6, 7]. As the teeth undergo secondary eruption, the gingival contour of anterior and posterior teeth undergo apical displacement, presumably from a decrease in sulcus depth and dentofacial growth [3, 6, 8, 9]. During the mixed dentition stage, the marginal gingiva around permanent teeth can appear more bulbous or prominent, because the gingiva is still attached to the crown and overlays the enamel [1].

Gingivitis in Children and Adolescents

Gingivitis is defined as the presence of gingival inflammation without bone loss or clinical attachment loss. Clinically, the inflamed gingiva may present with erythema, edema, gingival bleeding, and sometimes pain [10]. Genetics, demographics, socioeconomic status, and behavioral and clinical factors affect each individual’s
susceptibility to developing gingivitis [10]. However, gingivitis is almost universal in children and adolescents [7, 11-13].

Plaque accumulation on dental surfaces is strongly associated with the development of gingivitis [10, 12]. In one cross-sectional study, 3-year-olds with plaque accumulation were 28 times more likely to have gingivitis and 5-year-olds were 87 times more likely [12]. Plaque-induced gingivitis in children is more likely to appear clinically as swelling and a change in gingival color rather than bleeding and increased pocket depth [1]. Plaque adhered to dental surfaces for a long time can lead to the development of long standing gingivitis, characterized by gingival enlargement [1, 7]. Plaque-induced gingivitis is reversible in nature: improved oral hygiene and removal of plaque allow for a return in gingival health [11].

The prevalence of gingivitis increases with age, with notable peaks during puberty [1, 7, 10, 12-14]. Fluctuations in hormone levels during puberty can lead to an exaggerated gingival response even in the absence of increased plaque levels [1, 11]. Nonetheless, studies have shown that during puberty, plaque buildup is more directly associated with the development of puberty gingivitis than the presence of sex hormones, and oral hygiene is crucial to maintaining gingival health [15]. During puberty, there are also changes to the microbial community that may contribute to the onset of puberty gingivitis [16]. Other factors that can cause an individual to be predisposed to gingivitis are excessive overjet and overbite, nasal obstruction, mouth breathing habit, partially exfoliated or loose primary teeth, malpositioned or crowded teeth, and orthodontic appliances [1].
Microbial Cause of Plaque-Induced Gingivitis

Over 700 bacterial species inhabit the oral cavity by colonizing the hard and soft tissue structures within the mouth [17]. Healthy gingival tissues have a microbial profile consisting of mostly gram-positive and facultative bacteria, whereas gingival tissues with plaque-induced gingivitis have a more balanced microbial profile: there are only slightly more facultative than anaerobic bacteria, and slightly more gram positive than gram negative bacteria [17]. A study evaluating plaque samples of children in the 18- to 48-month age group demonstrated that most of these children had plaque containing at least one periodontal pathogen, such as *Porphyromonas gingivalis* and *Bacteroides forsythus* [18, 19]. Another study reported that 60% of children aged 2 to 18 years have plaque biofilms containing *P. gingivalis* and 75% have plaque biofilms containing *Aggregatibacter actinomycetemcomitans* [18]. The former bacteria are associated with gingivitis and the development of periodontitis [18]. Research on gingivitis in children have identified increased amounts of *Actinomyces, Capnocytophaga, Leptotrichia,* and *Selenomonas* in the subgingival microbiome [18]. Interestingly, these bacteria are typically not seen in plaque-induced gingivitis in adults [18].

Localized Juvenile Spongiotic Gingival Hyperplasia

Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a gingival condition first described in 2007 that commonly presents in children and adolescents. It has a 2.3:1 female predilection, although some studies have demonstrated a 50:50 tendency [20-22]. LJSGH lesions clinically present as painless, localized, or multifocal gingival overgrowths that are bright red, velvety or papillary in appearance, and bleed
easily [20, 21, 23, 24] (Figure 1). They develop preferentially in the anterior maxilla, along the facial gingiva of tooth roots or the interdental papilla [25]. Histopathologic features include papillary epithelial hyperplasia, loss of keratinization, spongiosis, and neutrophil exocytosis with an underlying vascular and inflamed lamina propria [20, 21, 25-27].

Figure 1. Clinical presentations of LJSGH

The etiology of LJSGH is unknown. Because of its papillary and occasionally exophytic presentation, researchers have investigated viral etiologies. A retrospective descriptive study ruled out human herpesvirus and polyomavirus as agents responsible for causing LJSGH [28]. Another retrospective study evaluating twenty-one cases of
LJSGH using p16INK4A immunochemistry and human papillomavirus polymerase chain reaction determined that the human papillomavirus does not play a direct role in the pathogenesis of LJSGH [22]. Interestingly, despite the absence of any detectable human papillomavirus DNA, LJSGH lesions exhibited increased p16INK4A expression [22]. P16INK4A is a tumor suppressor protein that is often used as a surrogate marker for human papillomavirus infections [29]. Its increased expression in LJSGH may be secondary to an intense, reactive inflammatory process [22].

Other etiologies have been suggested, but to date, the most viable explanation is ectopic junctional epithelium combined with a contributory inflammatory response [20, 21, 23, 27, 30]. Allon et al. conducted an immunohistochemical study that found that LJSGH lesions express similar cytokeratin patterns as junctional epithelium [23]. The displaced junctional epithelium lacks the protection that keratinized epithelium provides, thus making the gingiva more vulnerable to local irritation [20, 23, 27]. Other factors, such as local trauma, orthodontic treatment, tooth eruption, and local foreign body reaction may contribute to or maintain the inflammation [20, 21, 23, 25-27].

LJSGH is a benign gingival condition that may resolve spontaneously after a variable time period, and unlike plaque-induced gingivitis and puberty-associated gingivitis, it often persists despite improved oral hygiene [20]. Due to persistence and esthetic concerns, various treatment approaches have been used to treat LJSGH, including chlorhexidine application and laser ablation with topical steroid treatment. The majority of LJSGH cases reported in the literature have been treated with conservative
excision and debridement of the associated dental surfaces [21, 22, 26, 31]. Recurrence occurs in 6-25% of cases [20-22, 24].

Purpose

The overall objective of this research was to expound on the clinicopathological profile of LJSGH. Since LJSGH was first introduced in the dental literature, there has been a substantial increase in its diagnosis by dental professionals. However, the existing body of literature regarding LJSGH is scarce, with little known about what causes this gingival condition, and why it resolves spontaneously in some individuals while persisting and recurring in others. Understanding the pathogenesis of LJSGH is paramount to effectively treating patients presenting with LJSGH lesions, and to progress towards being able to prevent its occurrence.

By surveying the patients and/or parents of patients presenting with LJSGH, we expected to elucidate various factors that may be associated with the development of LJSGH. Furthermore, we compared the bacterial composition of the gingival crevicular fluid associated with an LJSGH lesion with that of a classic plaque-induced gingivitis site. Previous studies have ruled out human papillomavirus, human herpesvirus, and polyomavirus as etiological agents responsible for LJSGH [22, 28]. However, to date, no research has been conducted to determine if bacteria could be implicated in the development of LJSGH. LJSGH lesions, unlike gingival tissues affected by gingivitis, frequently persist despite improvement in oral hygiene and reduction in dental plaque levels. Therefore, we expected the bacterial microbiota associated LJSGH lesions to be different from that of plaque-induced gingivitis. Results in support of this hypothesis can
serve as a foundation for future studies aimed towards identifying a relationship between specific types or strains of bacteria and LJSGH.

By investigating whether various factors (i.e. demographics, presence or absence of mouth breathing, tooth brushing technique, etc.) are associated with LJSGH, this study can help direct future research towards a better understanding of what may contribute to or cause LJSGH. Furthermore, a comparison of the bacterial profiles of gingival crevicular fluid adjacent to LJSGH and classic gingivitis lesions may reveal whether a microbial influence should be further evaluated as possible etiologic agents in the development of LJSGH.
Chapter 2: Methods

Recruitment

Study participants with LJSGH were recruited at the Nationwide Children’s Hospital Dental Clinic from October 2016 to April 2017. Patients that met inclusion criteria (see below) were invited to return to the Dental Clinic to participate in this research study. Patients were continuously enrolled in the study until its conclusion. Parents and/or legal guardians provided written consent, and patients over 9 years of age provided written assent to participate in this study.

Inclusion and Exclusion Criteria

Inclusion criteria were American Society of Anesthesiologists classifications (ASA) I and II, English or Spanish speaking primary caregiver and patient, and possessing both plaque-induced gingivitis and LJSGH lesions. The Nationwide Children’s Hospital Dental Clinic employs a full time Spanish interpreter. Due to the readily accessible Spanish interpreting service, Spanish speaking primary caregivers and patients were included in the study. Exclusion criteria were previous treatment and resolution of LJSGH, uncooperative behavior, and inability to return for the second follow up visit.

Study Procedures: First Study Visit

This study consisted of two visits. At the first study visit, the patient/caregiver completed a written questionnaire that assessed patient demographics, home oral hygiene
regimen, general dental history, history of the LJSGH lesion, presence of any oral habits, pubertal status, and any significant medical problems that might not be included in the patient’s electronic patient record (Appendix A).

Gingival crevicular fluid was then sampled from the LJSGH lesion site and a plaque-induced gingivitis site, using coarse sterile paper points. The paper points were inserted into the facial gingival sulcus for approximately ten seconds, removed, and immediately placed in a stabilization buffer. The samples were frozen at \(-20^\circ\text{C}\) until they could be transported to The Ohio State University for bacterial DNA isolation and analysis.

One provider, TN, performed clinical examinations for all study participants. The clinical exam was performed after the gingival crevicular fluid sampling had taken place to minimize any disturbance that the examination might cause to the microbiota of the gingival crevicular fluid and gingival tissues. A standardized clinical data sheet was used to gather data about the size and location of the LJSGH lesion, the patient’s occlusion, presence of any potential factors that might have contributed to the development of LJSGH, and Silness and Löe gingival and plaque index scores (Table 1 and 2) [5]. Clinical photographs were also obtained of the LJSGH lesions.

<table>
<thead>
<tr>
<th>Scores</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal gingiva</td>
</tr>
<tr>
<td>1</td>
<td>Mild inflammation – slight change in color, slide edema. No bleeding on probing</td>
</tr>
<tr>
<td>2</td>
<td>Moderate inflammation – redness, edema, glazing. Bleeding on probing</td>
</tr>
<tr>
<td>3</td>
<td>Severe inflammation – marked redness and edema, ulceration. Tendency to spontaneous bleeding</td>
</tr>
</tbody>
</table>

Table 1. Silness and Löe Gingival Index Criteria, 1967
<table>
<thead>
<tr>
<th>Scores</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No plaque</td>
</tr>
<tr>
<td>1</td>
<td>A film of plaque adhering to the free gingival margin and adjacent area of tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface</td>
</tr>
<tr>
<td>2</td>
<td>Moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye</td>
</tr>
<tr>
<td>3</td>
<td>Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin</td>
</tr>
</tbody>
</table>

Table 2. Silness and Löe Plaque Index Criteria, 1967

All study participants were given the option to have the LJSGH lesion removed via excisional biopsy. The excisional biopsy was not part of the study, but was a treatment option for any patient who presents to Nationwide Children’s Hospital Dental Clinic with an LJSGH lesion. Participation in the study did not require that the patient receive this treatment because some examples of these inflammatory lesions resolve spontaneously. Likewise, patients could opt for the excisional biopsy without having to participate in the study. If the patient and his/her parent/caregiver chose an excisional biopsy, the oral pathology report was used as a histopathological confirmation of the clinical findings.

Study Procedures: Second Study Visit

Study participants returned 2-3 weeks after the initial study visit for a follow up. At this visit, information such as size of the LJSGH lesion and recurrence after biopsy (if applicable) were collected. Additionally, photographs were taken to visually document any changes to the LJSGH lesion. If the study participants elected to have the biopsy
completed at their first study visit, then the results of the surgical pathology report were reviewed with the child and parent/guardian at the second study visit.

Laboratory Methods

The laboratory methods for this study were completed according to the standard protocol in the Griffen-Leys Laboratory at The Ohio State University College of Dentistry. The standard protocol is described in detail below.

**16S rRNA Gene Sequencing:**

Thawed samples were homogenized with glass beads in a BeadBeater, and DNA was purified using a commercial kit (QiaAmp from Qiagen) without centrifugation of the sample. DNA was amplified using barcoded Human Microbiome Project universal primers that generate a 500+ base pair fragment containing the V1-3 hypervariable domain of the 16S rRNA gene. The primers were fused to adaptors specific for the MiSeq system that contain specific sequence key tags that enable multiplex sequencing. Accuprime-Pfx polymerase was used for 16S rRNA gene amplification, to minimize the risk of errors. The resulting bulk sequences were binned to individual oral samples based on the presence of key tags, and the sequences with low quality scores or were shorter than ~400 base pairs were filtered out.

Sequences were blasted against the CORE 16S rRNA reference database for identification [32] [available at http://www.microbiome.osu.edu]. Sequences that were not identified from this oral database were searched against the Human Oral Microbiome Database or the more comprehensive public databases, GenBank, SILVA, and RDP. Sequence counts were summed and normalized to obtain relative composition in percent
for all species present and also for higher-level taxa such as genus and phylum for each sample.

**Bacterial Analysis:**

Bray-Curtis multi-dimensional scaling was used for global bacterial community composition comparisons between the plaque-induced and LJSGH lesion samples. Differences between the bacterial communities were analyzed by PERMANOVA.

**Statistical Analysis**

Data were analyzed and reported descriptively as mean ± standard deviation. The Wilcoxon Signed Rank Test was used to determine if there was a difference in plaque index scores for plaque-induced gingivitis and LJSGH lesions. Statistical analysis was performed using Microsoft Excel 2011.

**Ethical Considerations**

The Nationwide Children’s Hospital Institutional Review Board approved this study (IRB16-00764). Prior to each participant’s enrollment in the study, signed informed consent was obtained from all parents/caregivers and signed informed assent was obtained from all patients nine years of age and older.
Chapter 3: Results

From October 2016 to April 2017, twenty-three patients (12.1 ± 3.05 years of age) presenting to Nationwide Children’s Hospital Dental Clinic were identified as having LJSGH. The patients identified with LJSGH were mostly female, with a 2.8:1 female to male ratio. With regards to race/ethnicity of the patients, 52% were Hispanic, 22% African-American, 17% Caucasian, 4% Asian, and 4% other. A number of patients declined participation in the study, did not meet inclusion criteria, were unable to be contacted, or did not present for their first or second study visits, and were thus excluded from the study. The remaining ten study participants enrolled in the study and presented for both the initial and follow up visits. All but one participant elected to have a biopsy at the first study visit. The one patient chose to have her biopsy completed at the second study visit. After review of the biopsy results, all had a histopathologic diagnosis of LJSGH. Only the study participants who had LJSGH and met all inclusion criteria (n=10) were included in the statistical and microbiological analyses.

Demographics

Of the 10 study patients, 60% were female, and the mean age was 12.5 ± 2.76 years. 80% of the patients identified themselves as Hispanic or Latino (Figure 2). All were healthy patients with no reported chronic medical or health conditions.
Figure 2. Race/Ethnicity of Study Participants

Questionnaire Results

The study participants themselves (30%), their mothers (30%), or their fathers (40%) completed the questionnaire at the first study visit. 90% of participants had seen a dentist within the past year, and 80% reported having a professional cleaning and dental examination at least every six months. All participants were aware that they had a red or swollen gum lesion that would not go away, with about half indicating that the LJSGH lesion has been present for more than a year (Figure 3). Five (50%) of the individuals who completed the questionnaire perceived that the LJSGH lesion had improved over time, four (40%) noticed no change, and one (10%) noticed worsening of the condition. More participants reported gingival bleeding when brushing than pain associated with the LJSGH lesion (Figure 4). All of the patients who reported LJSGH pain also reported gingival bleeding.
Figure 3. Duration of LJSGH

Figure 4. Reported Signs and Symptoms of Lesional Site
The remainder of the items on the questionnaire pertained to history of trauma, self-reported mouth breathing, home oral hygiene habits, oral habits, previous orthodontic treatment, consumption of foods that are potentially irritating to the gingiva, dental eruption issues, and onset of puberty. One (10%) of the study participants had trauma to the anterior teeth, but could not recall more specific information related to the incident. Most participants denied mouth breathing (Figure 5). Nine participants (90%) reported using a manual toothbrush and only one (10%) used an electric toothbrush. Table 3 depicts the frequency with which patients use mouthwash, toothpicks, floss, and brush their teeth. Some study participants were unable to recall what type of toothpaste they used, but Figure 6 illustrates the types that were reported on the questionnaire. All participants denied any specks, beads, sparkles, or other particles in their toothpastes. Regarding oral habits, two (20%) reported nail biting and two (20%) reported putting objects (i.e. pencils, toys, etc.) in their mouths (Figure 7). Five (50%) of patients stated that they did not use any type of lip products; the remaining 50% used a variety of lip products (i.e., Carmex (Carma Laboratories, Inc., Franklin, WI), Chapstick (Pfizer Consumer Healthcare, Richmond, VA), etc.). The questionnaire inquired about three types of foods that may cause gingival irritation: popcorn, nuts, and seeds. Most participants indicated that they frequently consumed popcorn; fewer reported eating nuts and seeds (Figure 8). Three (30%) had orthodontic treatment in the past involving the anterior teeth. Four (40%) of participants recall their anterior teeth taking a long time to erupt, but six (60%) did not have any teething problems (10% did, and 30% did not
know). Lastly, half of the participants reported that they were not experiencing puberty (Figure 9).

![Self-Reported Mouth Breathing](image)

**Figure 5. Self-Reported Mouth Breathing**

<table>
<thead>
<tr>
<th></th>
<th>Rarely</th>
<th>Once a day</th>
<th>Twice a day</th>
<th>More than twice a day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brush teeth</strong></td>
<td>1 (10%)</td>
<td>1 (10%)</td>
<td>7 (70%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><strong>Mouthwash</strong></td>
<td>2 (20%)</td>
<td>3 (30%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td><strong>Toothpicks</strong></td>
<td>8 (80%)</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Floss</strong></td>
<td>2 (20%)</td>
<td>5 (50%)</td>
<td>2 (20%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Table 3. Frequency of Home Oral Hygiene Habits**
Figure 6. Reported Toothpaste Type

Figure 7. Oral Habits
General Clinical Findings

One provider completed all clinical examinations with the aid of a dental assistant, who helped record the data. General dental characteristics, as well as clinical
findings specific to the LJSGH lesions, were noted. Where applicable, LJSGH lesions were compared to their plaque-induced gingivitis counterparts (within the same patient).

Molar and canine occlusion were highly variable amongst all study participants (Figure 10), with Class I relationships being the most common. The majority of participants did not have dry mouth, coated tongue, or a frenum attachment that extended to the attached gingiva of the alveolar crest (Figure 11). In contrast, seven (70%) of patients had lip incompetence (Figure 11). One (10%) participant was in active orthodontic treatment at the time of the study, while two (20%) participants have had previous orthodontic treatment.

![Canine and Molar Classifications](image)

Figure 10. Canine and Molar Classifications
Lesional Characteristics

All LJSGH lesions were erythematous. Six (60%) were flat and velvety, and four (40%) were papillary in appearance. Ten (100%) of the LJSGH lesions were located in the anterior sextant. Eight (80%) of the LJSGH lesions were found in the maxilla, one (10%) was found in the mandible, and one (10%) had LJSGH lesions in both the maxilla and mandible. Two (20%) of participants had multiple LJSGH lesions. Eight (80%) of teeth with LJSGH were fully erupted, while two (20%) were erupted with three-fourths of the crown clinically visible. The majority of teeth (60%) with LJSGH had a clinical defect (i.e. surface roughness, ditching) and/or supragingival calculus, both of which were detected with the tine of an explorer (Figure 12). Eight (80%) of the LJSGH sites bled upon probing. The average probing depths for the mesiofacial, midfacial, and distofacial LJSGH tooth sites were $2.64 \pm 0.81$ mm, $2.09 \pm 0.70$ mm, and $2.73 \pm 0.65$ mm.
respectively. The median plaque and gingival index scores for the study participants’ whole mouths were 1 and 1, respectively. When the plaque index of the tooth associated with the LJSGH lesion was compared to that of the plaque-induced gingivitis site (within the same individual), the median scores were 2 and 1, respectively. A Wilcoxon Signed Rank Test demonstrated that there was not sufficient evidence to suggest there was a significant difference in the plaque index scores of teeth associated with LJSGH versus those associated with the plaque-induced gingivitis sites ($\alpha = 0.05$). There was no difference in plaque scores between the teeth with LJSGH and the teeth with plaque-induced gingivitis.

Figure 12. LJSGH Tooth Characteristics
Biopsy Results and Follow Up

All study participants elected to have the LJSGH lesion removed via biopsy, which was submitted for histopathological analysis. 100% of the gingival samples were diagnosed microscopically as LJSGH on the surgical pathology reports. The average size of the LJSGH lesions before they were biopsied was $34.15 \pm 54.32 \text{ mm}^2$. Seven (70%) of the LJSGH lesions were removed via conservative excisional biopsies; the remaining lesions were too large to be completely removed, and thus incisional biopsies were performed. For patients who elected to have the biopsy performed at the first study visit, the average size of the LJSGH lesions was $25.11 \pm 48.87 \text{ mm}^2$ at the second or follow up study visit. Those lesions that were completely excised had a size of $0 \text{ mm}^2$ at the follow up study visit. None of the completely excised LJSGH lesions recurred at the follow up visit. Because one of the participants chose to have the biopsy completed at her second study visit, no information could be obtained about the size of her LJSGH lesion after the biopsy, and whether it recurred. Not surprisingly, the lesions that received incisional biopsies persisted at the follow up visit, but with smaller surface areas. None of the partially incised lesions increased in size over the study period.

Comparison of Subgingival Microbiomes

Gingival crevicular fluid was sampled from LJSGH sites and plaque-induced gingivitis sites, and analyzed for differences in the bacterial communities using the Bray-Curtis based non-metric multidimensional scaling technique (Figure 13). With the exception of a single outlier, the microbial communities belonging to LJSGH sites were interspersed amongst those belonging to the plaque-induced gingivitis sites. There was no
distinct separation between the microbiomes of LJSGH sites and plaque-induced gingivitis sites. A PERMANOVA analysis indicated there was no significant difference between the microbial communities of LJSGH sites and plaque-induced gingivitis sites.

Figure 13. Comparisons of Microbial Communities in LJSGH and Plaque-induced Gingivitis Sites

G = Plaque-induced gingivitis site
S = LJSGH site
Chapter 4: Discussion

The goal of this study was to explore clinical factors associated with the presence of LJSGH, and also to determine if certain bacteria predispose individuals to developing LJSGH. To achieve this means, study participants completed a questionnaire, received a clinical examination, and had gingival crevicular fluid sampled from their LJSGH site and a classic plaque-induced gingivitis site.

This study experienced a low participation rate with only 43.5% of those identified as having LJSGH at their dental appointments opting to participate fully in the study. One possible reason is that these lesions may not have been clinically large, symptomatic or unaesthetic for these patients and their guardians to want to seek additional treatment. Only 30% of the lesions were so large that they were not totally excised. Also noteworthy, is that 4.3% of the individuals recruited to participate in the study were clinically diagnosed with LJSGH at their dental appointment, only to have the lesion resolved by the time of the first study visit a few weeks later. This partially supports the conservative approach of watchful monitoring of LJSGH lesions [30], as some of them could spontaneously resolve without the need for surgical intervention. Those LJSGH lesions that persist for long periods of time despite improved oral hygiene warrant a biopsy for a definitive diagnosis. The demographics of this study group are mostly consistent with those previously published in the LJSGH literature [20, 21]. The average age of study participants was 12.5 years. Their ages ranged from 9 to 18 years,
reinforcing the “juvenile” characteristic of this lesion. However, other investigators have shown that LJSGH can manifest in adults as old as 84 years [28], thus warranting a consideration for deleting the descriptor of juvenile in the name of the lesion. Because our pediatric dental clinic limits the age of the patients being treated to less than 21 years-old, the results were skewed to a young age group. In this study, LJSGH occurred in 60% of females. This is not as high as the 2.3:1 female to male ratio reported by Chang et al, but is higher than the 1:1 ratio reported by Darling et al. [20, 21]. If all patients identified with LJSGH (i.e. not solely those individuals who chose to participate in the study) were taken into consideration, the female to male ratio was 2.8:1. This is more comparable to the findings of Chang et al. [21].

80% of participants in this study were Hispanic or Latino. This finding is contradictory to what was found by Chang et al. in 2008, who reported that 82% of their patients with LJSGH were Caucasian and only 14% were Hispanic [21]. It is unlikely that the discrepancy is due to a difference in the racial composition of Columbus, OH and Dallas, TX, where Chang et al. conducted their research. Demographic data from the 2010 census indicates that there are 5.6% and 42.4% individuals who are Hispanic or Latino in Columbus, OH and Dallas, TX, respectively [33, 34]. Based on population demographics alone, it would be more likely for the researchers at Baylor College of Dentistry to have a greater proportion of Hispanic or Latino patients presenting with LJSGH than at Nationwide Children’s Hospital. One possible explanation for the increased proportion of Hispanic individuals with LJSGH in this study is better access to care and the opportunity to obtain a surgical biopsy procedure. Or, it may be evidence
that Hispanics or Latinos are truly more susceptible to developing LJSGH, but this determination is speculative without further investigation of a larger study sample size.

**General Clinical Findings**

Despite 70% of participants reporting that they do not mouth breathe, 70% had lip incompetence upon clinical examination. The discrepancy may be due to an error in self-reporting, as the individual completing the questionnaire may not understand what mouth breathing means. 70% of individuals who completed the questionnaire were the parents of the study participants. Parents may not notice if their children are mouth breathers without additional explanation. Lip incompetence and mouth breathing most commonly affects the maxillary anterior sextant, and causes mucosal dryness, increased plaque levels, and gingival inflammation [35]. Chang et al. originally hypothesized that mouth breathing leads to dryness of the ectopic junctional epithelium, causing it to become inflamed and hyperplastic, and develop into LJSGH [21]. The high proportion of study participants exhibiting lip incompetence warrants further investigation into its potential influence on the pathogenesis of LJSGH. This may explain why LJSGH develops preferentially in the maxillary anterior sextant.

Chang et al. suggested that the development of LJSGH may be associated with children undergoing orthodontic treatment of the anterior teeth [21]. At the time of data collection, 30% have had or were in active orthodontic treatment involving the anterior sextants. Chang et al. reported fewer cases (15%) in which LJSGH developed after orthodontic treatment [21]. The difference in percentages may be attributed to reporting omissions from a retrospective analysis of archival material. It would appear that
orthodontic treatment may be a contributing factor in some children in the development of LJSGH, but more research must be done.

The median plaque and gingival index scores for the study participants were 1 and 1, respectively. If one were to categorize the Silness and Löe plaque and gingival index scores of 0, 1, 2, and 3 as none, mild, moderate, and severe, respectively, then all of the participants had mild plaque and gingivitis scores. There was no significant difference between the plaque scores of the LJSGH tooth site and the plaque-induced gingivitis tooth site. LJSGH is not an exuberant inflammatory response to plaque, as demonstrated by all participants having some level of generalized plaque throughout the dentition. LJSGH typically occurs in a more localized form [21]. Furthermore, most of the participants reported good oral hygiene (80% brush at least twice daily). If LJSGH were induced by plaque accumulation primarily, one would expect it to resolve with improved oral hygiene. These findings are supported by previously published literature that claim LJSGH is refractory to plaque reduction and improved oral hygiene [20, 21, 23].

Lesional Characteristics

All patients in this study presented with localized, brightly erythematous lesions on the facial gingiva. 60% of the lesions were flat and velvety, while 40% were papillary. 80% of the lesions bled easily with probing, and 80% developed preferentially in the anterior maxilla. These clinical presentations are consistent with what has been reported in the literature [20, 21]. Several publications have reported that LJSGH is a painless pathological entity [20, 21, 30]. The frequency of pain associated with LJSGH in this study was higher, with 30% of study participants reporting that their LJSGH lesions hurt.
This difference may be due to the smaller sample size of this study that may artificially inflate the true incidence of painful or symptomatic LJSGH lesions. Alternatively, the higher pain frequency could be more accurate of the proportion of LJSGH that are symptomatic since these patients were responding to the questionnaire while they still had the LJSGH lesion. Previous studies identified LJSGH cases from archival materials of their respective departmental institutions, and thus may have underestimated the prevalence of symptomatic LJSGH.

60% of the teeth associated with the LJSGH lesions had some form of a defect, such as surface roughness or enamel defect. It is possible that these defects could play a role in LJSGH formation by harboring gingival irritants (or acting as irritants themselves) and causing an inflammatory reaction and epithelial proliferation. Further research is necessary to explore any causal relationship between tooth surface defects and LJSGH.

All of the study participants elected to have their LJSGH lesions evaluated microscopically via an incisional or excisional biopsy. Small lesions (less than 7 mm in diameter) were completely removed and absent two to three weeks later at the follow up study visit. Those lesions that were larger persisted at the follow up visit which would be expected for an incisional biopsy. There is a decrease in lesion size after the biopsies were completed, justifying excisional or incisional biopsies as a treatment option for those individuals that wish to have their LJSGH lesions removed. Other reported treatment options are laser ablation followed by topical steroid application, with moderate resolution of the LJSGH lesion after the first round of laser ablation [26].
Potential Gingival Irritations

The questionnaire and clinical examination investigated potential sources of gingival irritation or other factors that may predispose an individual to LJSGH. The first domain to be evaluated was oral hygiene. The use of electric toothbrushes has steadily increased over the years. Similarly, the recognition and diagnosis of LJSGH has also increased since it was first described in 2007 [20]. One hypothesis was that the electric toothbrush could potentially be more irritating to the gingiva than a manual toothbrush, due to its oscillating and/or pulsating toothbrush head, thus increasing the likelihood that a patient may develop LJSGH. However, 90% of study participants reported using a manual toothbrush instead of an electric one. It is impossible to establish any causation conclusions based on prevalence, but it is reasonable to assume, based on the predominance of manual toothbrush users in this study, that the use of an electric toothbrush is unlikely to be related to the development of LJSGH. It is also unlikely that the toothpaste a patient uses is connected to LJSGH. Although most study participants were unable to recall or did not know what type of toothpaste they used in their oral hygiene regimen, none of them reported that their toothpastes contained sparkles, beads, or other particles that could be trapped into the inflamed tissues, resulting in chronic gingival irritation. Likewise, most of the participants do not regularly use mouthwash, toothpicks, or floss (i.e. more frequently than once a week), so these agents are most likely not associated to LJSGH.

Some have hypothesized that the etiology of LJSGH may be inflammation secondary to a localized foreign body [25]. Because of this, study participants were asked
to answer questions related to oral habits and the consumption of certain foods that may become lodged in the gingiva and cause a foreign body reaction. Regarding oral habits, only 20% reported nail biting, and 20% reported putting objects like pencils or toys in their mouths. With so few participants possessing some type of oral habit, LJSGH is probably not caused by or related to such habits as nail biting, digit sucking, or placing objects in the oral cavity. This makes sense, as most habits do not result in direct contact with the facial gingiva unless one was to “slip” and abrade the gingiva with a fingernail or other foreign object. The consumption of foods suspected of being traumatizing or irritating to the gingiva yield more compelling results. 60% of the participants with LJSGH frequently eat popcorn; fewer eat nuts or seeds. Popcorn hulls are notorious for becoming lodged in the marginal gingiva and causing irritation, or even periodontal abscesses [36]. Because the majority of study participants report frequent popcorn consumption, it is worth further investigation to determine whether it is correlated with the development and presence of LJSGH.

Some reports suggest that puberty may affect how the gingiva responds local trauma and irritation, leading to LJSGH [21, 30]. This is supported by the findings in this study, in which 80% of the participants were within the puberty age range (ten to fourteen years of age). Nonetheless, Darling et al. determined through immunohistochemical studies that their biopsied LJSGH lesions were negative for estrogen and progesterone receptors, and concluded that LJSGH is not likely influenced by the increases in sex hormones associated with puberty [20].
Comparison of Subgingival Microbiomes

To determine if there could be a bacterial etiology for LJSGH, gingival crevicular fluids of LJSGH associated teeth were sampled. The gingival crevicular fluid of a plaque-induced gingivitis site within that same individual was also sampled, to serve as an internal control. The bacterial communities were compared to determine if there was an underlying difference that may explain the development of LJSGH. The rationale was that if there is a true bacterial cause for LJSGH, the microbial analysis should reveal a trend or pattern that would warrant further research. However, the bacterial analysis yielded no difference between the microbiomes of LJSGH lesions and those of plaque-induced gingivitis sites. It is, therefore, unlikely that bacteria are responsible for the etiology of LJSGH.

Interestingly, there was one individual whose LJSGH gingival crevicular fluid sample was an outlier compared to other LJSGH and plaque-induced gingivitis samples. The outlier sample belonged to a fifteen-year-old Hispanic female who presented with generalized mild supragingival calculus deposits. The periodontal probing depths of her LJSGH-associated tooth were within normal limits. Bacterial analysis of her LJSGH gingival crevicular fluid revealed bacteria typical of chronic periodontal infections: *Porphyromonas gingivalis* (37%), *Fusobacterium nucleatunem* (8%), *Tannerella forsythia* (5%), *Treponema denticola* (3%), and *Capnocytophaga sputigena* (3%).

Differential Diagnosis

LJSGH may be subject to misdiagnosis, as it predominantly occurs in the same age group as puberty-associated gingivitis and may appear clinically similar to other
localized gingival lesions [20, 30]. This is at least partially responsible for the underreporting of LJSGH in the literature until recently. Other pathological entities that need to be ruled out from the differential diagnosis include: pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, plasma cell gingivitis, and foreign body gingivitis. Distinguishing features of pyogenic granuloma are its: peak incidence in the third and fourth decades of life, rapid growth, pedunculated appearance, and friable surface that may ulcerate [27, 30, 37]. Peripheral giant cell granuloma, which typically present in adults, is more violaceous than LJSGH lesions, tend to be pedunculated and ulcerated, and is more common in the mandible, as opposed to the maxilla [27, 37]. Peripheral ossifying fibroma frequently occurs in the maxilla, and affects females in their second decade [37]. It has a recurrence rate of 16% [37]. Plasma cell gingivitis represents a contact allergy. It is characterized by a generalized loss of normal stippling and the affected tissues are tender and sensitive [37]. Foreign body gingivitis is an inflammatory reaction to a foreign material that is entrapped within gingival tissues [27]. It can be located in both the anterior and posterior sextants, has a strong female predilection, usually presents in the middle-aged adult, and is associated with pain [27]. In this study another entity has a clinical appearance that is very similar to LJSGH and this is the rare entity, superficial gingival lymphangioma. A patient in the present study had to be excluded because the biopsied tissue was diagnosed as this vascular malformation [38]. A thorough clinical examination and history, along with histopathological analysis, allows for the definitive diagnosis of LJSGH.
Limitations

There are several limitations to this study: First, the questionnaire results rely primarily on what the patient and/or their parents or guardians answer. The questionnaire responses are subject to recall bias and rely on the answerer knowing and recalling very specific details about the study participants’ dental history and the clinical history of LJSGH. Furthermore, the questions asked may inadvertently cause the respondent to feel pressured to select the answer that they think should be correct or least embarrassing, as opposed to the answer that is most applicable to him/her. A second limitation to this study is the small sample size. If the sample size had been larger, there would have been greater statistical power to draw conclusions and to better identify statistically significant results. Lastly, the study was limited by the short follow up period. At two to three weeks’ follow up, none of the LJSGH lesions with excisional biopsies recurred. It would be beneficial to continue following these patients for a longer period of time (i.e. six months to a year), to determine recurrence rates at longer intervals.
Chapter 5: Conclusion

LJSGH is an inflammatory gingival disease that is being increasingly recognized by oral healthcare providers as its own separate entity. Because it was only introduced in 2007 by Darling et al., very little has been published on this topic [20]. This study aimed to contribute to the existing body of research on LJSGH by 1) identifying potential risk factors for the development of LJSGH and 2) determining if there is a difference in the bacterial communities of LJSGH lesions versus plaque-induced gingivitis. The findings from this study are consistent with previous literature: LJSGH had a slight female predilection, and occurred primarily in the preadolescent age group. It developed preferentially in the maxillary anterior sextant, and was associated with gingival bleeding. The subgingival bacterial communities of LJSGH lesions were not significantly different from those of classic plaque-induced gingivitis lesions. Further research is necessary to demonstrate a statistically significant relationship between LJSGH and Hispanic predominance, lip incompetence, dental defects, and trauma from food.
References


Appendix A: LJSGH Parent/Patient Questionnaire
1. What is the patient’s race/ethnicity?
   a. African-American
   b. White or Caucasian
   c. Asian or Pacific Islander
   d. Hispanic or Latino
   e. Native American or American Indian
   f. Somali
   g. Other: (please specify) ____________________________________________________________________

2. What is your relationship to the patient?
   a. Self (I am the patient)
   b. Mother
   c. Father
   d. Grandparent
   e. Sibling
   f. Aunt/Uncle
   g. Foster parent
   h. Other: (please specify) ____________________________________________________________________

3. Has your child seen a dentist within the past 12 months?
   a. No
   b. Yes

4. How many times a year does your child get a dental check up with a tooth cleaning?
   a. Less than once a year
   b. Once every 12 months
   c. Once every 6 months
   d. Once every 3 months
   e. Other: (please specify) ____________________________________________________________________

5. Has your child been diagnosed with a chronic medical condition?
   a. No
   b. Yes

6. Does your child have a redness or swelling of the gums that does not go away? (If selecting a or c, please skip to question 10)
   a. No
   b. Yes
   c. I don’t know

7. How long has this redness or swelling been on your child’s gums?
   a. Less than 1 month
   b. 1-3 months
   c. 4-6 months
   d. 7-9 months
   e. 10-12 months
   f. Over a year

8. Do you feel that the redness or swelling has:
   a. Gotten worse over time
9. Does this redness or swelling hurt?
   a. No
   b. Yes

10. Do the gums bleed when your child brushes his/her teeth?
    a. No
    b. Yes

11. Has your child ever had an injury to his/her front teeth?
    a. No (If no, skip to question 15)
    b. Yes

12. Were any of the front teeth loose after the injury?
    a. No
    b. Yes

13. Was there any bleeding associated with the dental injury?
    a. No
    b. Yes

14. If yes, how long ago was the injury?
    a. Within the past 6 months
    b. Between 6 months and a year ago
    c. More than a year ago

15. Does your child breath through his/her mouth with his/her lips apart?
    a. No
    b. Yes, rarely
    c. Yes, sometimes
    d. Yes, most of the time
    e. I don’t know

16. How often does your child brush his/her teeth?
    a. Rarely
    b. Once a day
    c. Twice a day
    d. More than twice day

17. What type of toothbrush does your child use?
    a. Manual toothbrush
    b. Battery toothbrush
    c. Electric toothbrush
    d. Other: (Please specify) _________________________

18. What type of toothpaste does your child use? Select all that apply.
    a. Fluoride toothpaste
    b. Toothpaste for sensitive teeth
    c. Anti-tartar toothpaste
    d. Tooth whitening toothpaste
    e. Other: (Please specify) _________________________

19. How often does your child use floss?
a. Never  
b. Rarely  
c. At least once a month  
d. At least once a week  
e. Daily  

20. How often does your child use toothpicks?
   a. Never  
b. Rarely  
c. At least once a month  
d. At least once a week  
e. Daily  

21. How often does your child use mouthwash?
   a. Never  
b. Rarely  
c. At least once a month  
d. At least once a week  
e. Daily  

22. Does your child use any lip products?
   a. No  
b. Yes  
c. I don’t know  

23. Does your child have any of the following habits? Select all that apply.
   a. Nail biting  
b. Thumb or finger sucking habit  
c. Cheek chewing  
d. Putting things in their mouth (i.e. pencils, toys, etc.)  
e. Other: (Please specify) _______________________

24. Has your child ever had braces?
   a. No  
b. Yes  

25. If yes, were there braces on the front teeth?
   a. No  
b. Yes  

26. Does your child frequently eat the following foods? Select all that apply.
   a. Popcorn  
b. Nuts  
c. Seeds  
d. None of the above  

27. Did it take a long time for the front teeth to come in?
   a. No  
b. Yes  
c. I don’t know  

28. Did your child have any teething problems?
   a. No  

b. Yes
   c. I don’t know

29. Is your child going through puberty?
   a. No
   b. Yes
   c. I don’t know
Appendix B: Summary of Study Participants’ LJSGH Data
<table>
<thead>
<tr>
<th>Participant</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Race or Ethnicity</th>
<th>Tooth Site</th>
<th>Initial Size (mm)</th>
<th>Treatment</th>
<th>Follow Up Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>Male</td>
<td>Hispanic or Latino</td>
<td>#9</td>
<td>15x6</td>
<td>Incisional biopsy</td>
<td>12x6</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>Female</td>
<td>Hispanic or Latino</td>
<td>#7</td>
<td>3x1.5</td>
<td>Excisional biopsy</td>
<td>0x0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Female</td>
<td>Hispanic or Latino</td>
<td>#7 and #24</td>
<td>3x1 and 6x2</td>
<td>Excisional biopsy for #7, none for #24</td>
<td>0x0 and 6x2</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Male</td>
<td>Hispanic or Latino</td>
<td>#11</td>
<td>10x2</td>
<td>Incisional biopsy</td>
<td>6x3</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>Female</td>
<td>Hispanic or Latino</td>
<td>#8</td>
<td>2x3</td>
<td>Excisional biopsy</td>
<td>0x0</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>Male</td>
<td>Hispanic or Latino</td>
<td>#8</td>
<td>2x2</td>
<td>Excisional biopsy</td>
<td>0x0</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>Female</td>
<td>Hispanic or Latino</td>
<td>#11</td>
<td>17x10</td>
<td>Incisional biopsy</td>
<td>17x8</td>
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<tr>
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<td>15</td>
<td>Female</td>
<td>Hispanic or Latino</td>
<td>#6</td>
<td>7x3</td>
<td>Excisional biopsy</td>
<td>0x0</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>Male</td>
<td>African American</td>
<td>#22 and 24</td>
<td>3x5 and 7x3</td>
<td>Excisional biopsy for #22, none for #24</td>
<td>0x0 and 6x3</td>
</tr>
<tr>
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<td>14</td>
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<td>Asian</td>
<td>#8</td>
<td>4x2</td>
<td>Excisional biopsy</td>
<td>0x0</td>
</tr>
</tbody>
</table>

Table 4. Summary of Study Participants’ LJSGH Data