Longitudinal Craniofacial Growth in Pierre Robin Sequence in Comparison with Isolated Cleft Palate and Unaffected children

By

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Abstract

Background: Pierre Robin Sequence (PRS) is defined at birth by the presence of mandibular micrognathia, glossoptosis and airway insufficiency with or without cleft palate.

Objectives/hypothesis: Analyze craniofacial morphology and facial growth patterns in non-syndromic PRS and compare them to isolated cleft palate (ICP) and unaffected children. Materials & Methods: Craniofacial characteristics were examined at three time points by comparing digitized tracings of subjects with PRS and ICP and unaffected class I subjects. Between-group and longitudinal differences across the time points were analyzed. Results: PRS and ICP groups had significantly small maxillae compared to the unaffected group and displayed a vertical pattern of growth. PRS group had the smallest mandibles (by 8%; 9.7mm) followed by the ICP group (by 4%; 4.2mm) when compared to the unaffected group. Conclusions: Craniofacial morphology and longitudinal facial growth in subjects with PRS and ICP are similar in many areas but differ significantly from comparable unaffected children.
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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>BGC</td>
<td>Burlington Growth Centre</td>
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<tr>
<td>EMD</td>
<td>Estimated mean difference</td>
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<tr>
<td>HSC</td>
<td>Hospital for Sick Children</td>
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<td>ICCC</td>
<td>Intra-class Correlation Coefficient</td>
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<td>ICP</td>
<td>Isolated cleft palate</td>
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<td>OSA</td>
<td>Obstructive sleep apnea</td>
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<td>Pre-epiglottic baton plate</td>
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<td>PRS</td>
<td>Pierre Robin Sequence</td>
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<td>UAO</td>
<td>Upper airway obstruction</td>
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1. Introduction and Statement of the Problem

1.1 Introduction

Craniofacial anomalies relate to abnormalities in growth patterns and development of the face and the skull. Development of these abnormalities can primarily be attributed to interruptions in the normal embryonic growth process occurring in utero, resulting in defects seen at birth. They can also occur secondary to trauma or pathologic processes that occur after birth (Figueroa and Friede, 2000). Pierre Robin Sequence (PRS) is a craniofacial disorder defined at birth by the presence of a core triad - mandibular micrognathia, glossoptosis and upper airway obstruction (Robin, 1934). Although the presence of palatal clefting is not necessary for the diagnosis of PRS, it is present in 84.5% to 95% of these patients (Latham and Van der Molen, 1966, Anderson et al, 2011; van Lieshout et al, 2014). This condition is referred to as a ‘sequence’ because the primary anomaly of a micrognathic mandible sets into motion a cascade of events that gives PRS its characteristic features. The small mandible prevents the tongue from descending adequately during the fusion of the palatal shelves resulting in a cleft in the palate (Opitz, 1979). The small mandible is also unable to provide adequate space and support for the tongue musculature resulting in glossoptosis and a congested airway, often requiring emergency airway management in the delivery room (Robin, 1934; Opitz, 1979).

The incidence of PRS reported in the literature varies between 1 in 8,500 and 1 in 20,000 births, making it a rare condition (Bush, 1983; Printzlau and Anderson, 2004). The characteristic micrognathic mandible of PRS is etiologically heterogeneous and can result from either an intrinsic dysplasia or secondary to intrauterine compression and teratogenic influences during fetal development (Poswillo, 1966; Cohen, 1999). Recent developments in genetic testing have revealed numerous genetic associations that can lead to PRS, where it may form part of a larger syndrome such as, Stickler syndrome or Treacher Collins syndrome. Although the exact genetic causes of PRS as a non-syndromic anomaly are not yet known, its occurrence has been associated with a family history of clefting in 27% of cases (Jakobson et al, 2006).
In syndromic PRS, because the etiology is usually intrinsic and related to genetic defects, the ability of the mandible to ‘catch-up’ to normal is reported to be quite limited (Shprintzen, 1992). In non-syndromic PRS, because the etiology was thought to be mostly extrinsic, mandibular growth was expected to improve significantly and attain normal or near normal lengths. This is not the case as reported widely in the literature (Randall et al., 1965; Shen et al., 2012). In the time immediately following birth, infants with PRS do show an accelerated percentage of growth, however, this is not enough to ‘catch-up’ to normal and completely resolve the retrognathic and convex profile retained into adulthood (Figueroa et al., 1991; Vegter et al., 1999; Hermann et al., 2003; Erikson et al., 2006).

In the literature, PRS is often compared to isolated cleft palate groups (ICP) in order to take into consideration the effect of the cleft palate and its surgical repair on growth of the facial skeleton and overall craniofacial morphology (Figueroa et al., 1991). It is known that the maxillary lengths of subjects with palatal clefts are smaller than normal (Shibasaki and Ross, 1969; Laitinen and Ranta, 1998). Some studies suggest that the deficiency in length is due to post-surgical scar tissue formation since un-operated subjects are reported to have maxillas that are comparable to normal (Ortiz-Monasterio et al., 1966; Mars and Houston, 1990). Others suggest that the deficiency in maxillary length is a combination of an innate developmental defect in addition to the surgical cleft repair, since un-operated subjects had maxillas that were smaller than normal (Coupe and Subtelny, 1960; Ross and Coupe, 1965; Capelozza et al., 1993). Bishara (1973) and daSilva et al. (1989, 1992) found no significant differences in the maxillary lengths of patients with ICP that received surgical cleft repair compared to those that did not receive surgery, suggesting that the deficiency in maxillary length might be due to an innate developmental defect.

The effect of cleft palate on the mandible is also a subject of controversy. Some studies have refuted a significant influence of the cleft palate repair on morphology and spatial positioning of the mandible (Bishara, 1973; daSilva et al., 1992). However, other studies show that the presence of palatal clefting and the repair thereof, does have an effect on mandibular growth. Shibasaki and Ross (1969) compared patients with ICP to normal subjects and found that although patients with ICP have normal mandibular lengths, their mandibles are posteriorly
rotated resulting in a large gonial angle. However, rat studies as well as human studies have shown that the mandibular growth pattern is normal but the length of the mandible is shorter than normal (Warkany et al., 1943; Warkany and Schraffenberger, 1947; Borden 1957).

A review of the literature comparing PRS and ICP suggests that there is a difference in the rate of craniofacial growth and morphology when paralleling to each other and to unaffected subjects. Although PRS and ICP have mandibles that might have some morphogenetic similarities, PRS have mandibles that are smaller, both in body length and ramus height, more retrognathically positioned and posteriorly rotated leading to a soft tissue profile that is more convex than ICP (Laitinen and Ranta, 1992). The pattern of growth also tends to be more vertical as suggested by steeper mandibular plane angles in subjects with PRS (Laitinen and Ranta, 1992; Daskalogiannakis et al., 2001).

Aside from a micrognathic mandible when comparing to unaffected children, patients with PRS have been shown to have a smaller maxilla with a steep palatal plane angle and smaller cranial base lengths (Suri et al., 2010a). The detailed analysis of craniofacial morphology of PRS conducted by Suri et al. (2010a) provides a quantitative comparison between patients with PRS and unaffected children. A custom comprehensive cephalometric analysis using internal landmarks as well as conventional landmarks were used for this study (Suri et al., 2006, 2010b). The mandible in subjects with PRS was found to be 6° retrognathic, 10° steeper and 6.5% shorter in length than unaffected normal children. As well, the maxilla in subjects with PRS was found to be 12% shorter than normal subjects. This information is clinically relevant in order to accurately plan both orthodontic and surgical treatment that is often required in patients with PRS. It is important to note how this detailed analysis of PRS craniofacial morphology compares to that of ICP craniofacial morphology, in order to identify the role that the cleft palate and its repair might play on growth of the craniofacial complex. This will help not only to verify the ideology that patients with PRS present with a more severe but morphogenetically similar developmental anomaly as those with ICP, but also allow us to learn more about the specific differences between ICP and normal
1.2 Statement of the Problem

Although PRS is a well-recognized craniofacial anomaly, several aspects of this condition still remain poorly understood. Till date, PRS has several definitions and agreed-on clinical features, making comparisons of the results in the literature, a difficult task (Breugem et al., 2016). Most of what is known regarding the craniofacial growth and morphology of children and adolescents with PRS is based on small sample sizes, case reports, mixed racial samples, cross sectional studies, short-term longitudinal studies and mixed longitudinal studies. As well, some studies have used mixed groups of syndromic and non-syndromic PRS. Rogers et al (2009) reported that mandibular morphology and position varies depending on the association of PRS with a syndrome, as well as the type of syndrome that is present. All of these factors have introduced variability in the results reported in the literature, limiting its applicability to treatment of all patients with PRS. It is important to understand craniofacial growth and morphology in this group of patients in order to confidently plan and execute dentofacial treatment.

In order to shed some light on the craniofacial growth patterns of patients with PRS, the aim of this study was to evaluate and identify differences in craniofacial morphology and growth patterns in patients diagnosed with non-syndromic PRS in comparison with patients diagnosed with isolated cleft palate and unaffected subjects. This evaluation was to be carried out by using the comprehensive cephalometric analysis reported by Suri et al. (2006, 2010b) focussing on regional detail with internal landmarks.
2. Review of the literature

2.1 Pierre Robin Sequence (PRS)

This craniofacial disorder is named after the French stomatologist, Pierre Robin, who described its defining features in 1923. Previous associations between micrognathia and airway obstruction were described as early as 1822 by St-Hilaire, followed by Fairbain in 1846 and Shukowsky in 1911 (Scott and Mader, 2014). However, Pierre Robin was able to identify that the respiratory difficulties experienced by infants and children with hypoplastic mandibles were due to glossoptosis. In his initial observations of 6-7 year old children with retruded mandibles, he found that even after adenoidectomies, they still experienced breathing difficulties. He explained that retracted mandibles caused the base of the tongue to be pushed back against the epiglottis, creating an airway obstruction. As soon as their mandibles were forced forward, these children were able to breathe with ease. He also observed that in some extreme cases, babies born with severely hypoplastic mandibles did not survive past 16 to 18 months due to breathing and feeding difficulties. He called this mechanical effect “glossoptosis” and the condition, “glossoptotic syndrome” (Robin, 1934). By the 1960s, other clinicians added further information through their own observations, and it began to be called Pierre Robin Syndrome (Randall, 1965; Shprintzen, 1992). Over the years, several terms have been used to diagnose this condition including, Robin Syndrome, Robin Anomalad and, Pierre Robin Triad. More recently it has been described as a sequence rather than a syndrome because the abnormal mandible begins a cascade of events that leads to the characteristic features of this condition (Opitz, 1979; Cohen, 1981).

Aside from the varied nomenclatures used to identify this condition, there is universal confusion with regard to the key characteristic features that define PRS making diagnosis difficult (Van der Haven et al, 1997; Breugem and Van der Molen, 2009). Today, the all-encompassing definition for PRS is, a craniofacial disorder diagnosed at birth by the presence of a core triad of mandibular micrognathia or retrognathia, glossoptosis and upper airway obstruction with or without cleft palate (Breugem et al, 2016). Although the presence of palatal clefting is not necessary for the diagnosis of PRS, it has been reported to be present in 84.5% to 95% of these patients (Latham and Van der Molen, 1966, Anderson et al, 2011; van Lieshout et al, 2014).
Even though micrognathia is a key feature of this condition, a specific definition for what constitutes micrognathia is lacking in the literature and is currently based on subjective criteria (Izumi et al., 2012).

2.1.1. Prevalence

Pierre Robin Sequence is a relatively rare disorder with a reported prevalence range of 1 in 8,500 to 1 in 20,000 live births (Bush, 1983; Printzlau and Anderson, 2004). The wide range in prevalence reported in the literature can be attributed to the pathogenetic and phenotypic variability of the condition making it difficult to clearly define and diagnose this disorder. As well, prevalence has been shown to differ in various populations and racial groups (Basart et al., 2015; Cohen, 2001). Asians are reported to have the lowest prevalence, while Caucasians are reported as having the highest prevalence of PRS (Tolarova and Cervenka, 1998). In terms of a gender related predilection, there is no difference in incidence of PRS reported in males and females (Printzlau and Anderson, 2004).

PRS is commonly classified as a syndromic or non-syndromic entity. In syndromic PRS, the triad of features forms part of a larger syndrome accounting for 35% of PRS cases (Holder-Espinasse et al., 2001). There are over 40 syndromes associated with PRS, the most common of which are Stickler Syndrome (44%), velocardiofacial Syndrome (7%), Treacher Collins Syndrome (5%) and craniofacial microsomia (3%) (Evan et al., 2006; Rogers et al., 2009; Evans et al., 2011). Other associated syndromes include 22q11.2 deletion syndrome, Marshall syndrome, Van der Woude syndrome, oculo-auricular-vertebral spectrum, Moebius syndrome, and Nager syndrome (Izumi et al., 2012). It can also be associated with environmentally-induced or teratogenic syndromes such as Fetal Alcohol Syndrome and Fetal Hydantoin Syndrome (Gorlin et al., 1990). In non-syndromic PRS, the triad of features may occur in isolation, as it does in 48% of cases. It may also occur in association with a wide spectrum of anomalies involving the eyes and/or ears, as it does in 17% of cases (Holder-Espinasse et al., 2001; Ozcan et al., 2004).

There is a possibility that cases of syndromic PRS have been underreported in the literature because a syndromic diagnosis is often difficult to make in the neonatal period (Al-Samkari et al,
Change in diagnosis from non-syndromic to syndromic PRS often occurs after the neonatal period because syndrome-specific facial features and syndrome-specific medical complications are rarely noted during this time, becoming more pronounced with growth. As well, in order to accurately diagnose a patient with syndromic or non-syndromic PRS, genetic testing, family history, prenatal exposure to teratogenic agents as well as ophthalmologic and audiologic evaluations are necessary, which might be difficult to do during the neonatal period (Izumi et al., 2012). In terms of treatment, it is important to make this distinction as patients with syndromic PRS typically require more aggressive airway and feeding management than patients with non-syndromic PRS (Al-Samkari et al., 2010; Izumi et al., 2012).

2.1.2. Etiology

Pierre Robin Sequence is known as an etiologically heterogeneous condition. The characteristic mandibular micrognathia can occur as a result of inherent defects in mandibular outgrowth and elongation due to genetic aberrations. It can also occur from causes that are external to the mandible but secondarily impact its growth during fetal development. These interruptions can be caused by intrauterine compression and restriction of mandibular growth or by the influence of environmental teratogens (Poswillo, 1966; Cohen, 1999; Tan et al., 2013).

There are several instances that point to the genetic etiology of PRS. Family members of patients with PRS often have cleft lip or palate (Marques et al., 1998; Holder-Espinasse et al., 2001). As well, PRS may be associated with other syndromes that have a genetic basis such as Stickler syndrome, velo-cardio-facial syndrome and Treacher Collins syndrome, suggesting that syndromic PRS is due to aberrations in the patient’s genetic make-up (Evans et al., 2006). PRS has been linked to SOX9 enhancer deletions (17q24.3–q25.1), rearrangements of certain chromosome loci such as, 2q24.1–q33.3 (GAD67), 4q32-ter, 11q21–q23.1 (PVRL1) and (SOX9) and, mutations in collagen genes such as, COL2A1 and COL11A1 (Cohen, 1999; Jakobsen et al., 2006).

Non-genetic causes of PRS have been linked to intrauterine constriction, oligohydranmios, breech position, abnormal uterine anatomy, or multiple births (Jakobsen et al., 2006; Amarillo et al., 2013). In any of these situations, the posture of the embryo is altered such that the normal
extension of the cervical spine that occurs after the 6th week is prevented, delayed or greatly reduced, interfering with development of normal cranial flexure. The chin becomes compressed against the sternum, forcing the mandible against the nasal capsular region and arresting intramembranous ossification of the body of the mandible (Poswillo, 1966). Furthermore, teratogens such as alcohol, tobacco, and drugs such as tamoxifen have been implicated in the development of Pierre Robin Syndrome (Prows and Bender, 1999; Holder – Espinasse et al, 2001; Berger and Clericuzio, 2008).

2.1.3. Embryopathogenesis

In the early 4th week of embryonic development, neural crest cells that originate in the mid- and hindbrain regions of the neural folds migrate into the future head and neck regions to initiate formation of the branchial arches (Praveen and Barbara, 2007). It is the first branchial arch that gives rise to the cartilage and bones of the mandibular skeleton. Mandibular hypoplasia can result from insufficient or defective neural crest cell production or migration into the first branchial arch during the 4th week of embryonic development (Praveen and Barbara, 2007). In between the 7th and 11th weeks, the presence of a hypoplastic mandible sets into motion the sequence of events that produces the characteristic features of this craniofacial condition (Figueroa et al, 1991). Normally, during the 7th week of embryological development, the tongue migrates downward as the mandible continues to develop allowing the secondary palatal shelves to elevate and begin fusion from the anterior end by the 9th week to the posterior end by the 12th week (Ferguson, 1988; Gorlin et al, 1990). In a fetus with a hypoplastic mandible, there is inadequate space and support for the tongue musculature resulting in an elevated and retruded tongue posture or glossoptosis. The elevated tongue posture prevents fusion of the palatal shelves, resulting in a cleft in the palate, while the retruded tongue position blocks the pharyngeal space resulting in varying degrees of airway obstruction (Shen et al, 2012). Normal palatal closure occurs in a ‘zipperlike’ manner from the anterior aspect to the posterior aspect of the palate. Thus, if a primary failure of fusion occurs, it should result in a V-shaped defect, as it does in patients with isolated cleft palate. However, in patients with PRS, majority exhibit U-shaped clefts that are generally wider and longer than patients with isolated cleft palate due to the mechanical interference of palatal closure provided by the elevated tongue posture (Latham and Van der Molen, 1966; Printzlau and Anderson, 2004; Godbout et al, 2014).
2.1.4. Management

Mortality rates in patients with PRS range from 5% to 30% and is mainly attributed to upper airway obstruction (UAO) (Robin, 1934; Caouette-Laberge et al., 1994). Along with UAO, the presence of the cleft palate and primary oropharyngeal dysmotility impairs the infant’s ability to feed and often leads to gastroesophageal reflux, aspiration and malnutrition (Baudon et al., 2002; Kochel et al., 2011). Supplemental tube feedings are often required and initially given through nasogastric tubes. In cases with persistent and chronic feeding difficulties, a surgically placed gastronomy tube is used (Cohen et al., 2017). Gastroenterologists and feeding specialists monitor the infant to ensure adequate nutrition, management of gastroesophageal reflux, good pulmonary protection from aspiration and adequate development during the first years of life.

In order to improve the infant’s chances of survival and maintain adequate nutrition, upper airway obstruction, which is most significant during the first 8 weeks of life, requires continuous monitoring by neonatologists, pediatricians and sleep medicine professionals (Daniel et al, 2013; Cohen et al, 2017). The obstruction is not always caused by glossoptosis alone, as previously thought by Pierre Robin. It is multifactorial, related to anatomical abnormalities of the mandible, impaired function of the genioglossus in holding the tongue out of the pharyngeal space and neuromuscular function of the pharynx (Sher, 1992). Nasopharyngoscopy studies show that airway obstructions can be classified into four types depending on the cause: type 1 is posterior movement of the dorsum of the tongue against the posterior pharyngeal wall, type 2 is posterior movement of the tongue compressing the soft palate, type 3 is medial collapse of the lateral pharyngeal wall and type 4 is sphincteric constriction of the pharynx (Sher, 1986). The method and success of the airway management strategy depends on the type of airway obstruction present in the patient. Patients with isolated PRS often display type 1 and/or type 2 obstructions, while syndromic patients can display all four types of obstruction, making airway management a challenge (Sher, 1992).

The consequences of UAO range from hypoxia to cor pulmonale, neurodevelopmental delay, failure to thrive and sudden death (Bacher et al, 2011). Some infants can maintain a patent airway while awake but fail to do so during sleep, thus developing obstructive sleep apnea (OSA). Others may not be able to maintain a patent airway when awake or asleep and require
more aggressive management (Sher, 1992). Although evidence based management recommendations are lacking in the literature and treatment is mainly carried out based on institutional preferences, some basic recommendations do exist. The first step in airway management involves conservative strategies such as prone positioning and placement of nasopharyngeal tubes, both of which have shown a success rate of 45-69.2% (Caouette-Laberge et al, 1994; Kirschner et al, 2003). Surgical interventions might be required for severe cases and include procedures such as tongue-lip adhesion, mandibular traction, and mandibular distraction osteogenesis, with the most aggressive intervention being tracheostomy (Evans et al, 2006; Izumi et al, 2012). Continuous positive airway pressure (CPAP) can also be used in the management of OSA. Oral appliances such as the pre-epiglottic baton plate with velar extension (PEBP) supports the pharyngeal wall and shifts the base of the tongue forward, widening the hypopharyngeal space and improving the ability to breathe (Kochel et al, 2011). These appliances have been shown to be an effective treatment strategy for respiratory distress, feeding difficulties and OSA management (Hotz and Gnoinski, 1982; Oktay et al, 2006; Bacher et al, 2011, Müller-Hagedorn et al, 2017). A randomized clinical trial by Buchenau et al (2007) showed that apnea index was reduced by 70% in patients given the PEBP appliance.

During the first few months of post-natal life, the mandibles of some infants will grow improving tongue position along with maturation of pharyngeal neuromuscular function which helps in resolution of the airway and feeding insufficiencies (Sher, 1992). In most isolated, non-syndromic cases, 6-8 weeks of intervention is adequate because of the catch-up mandibular growth that occurs during this time (Pruzansky and Richmond, 1954; Sher 1992). However, in other cases that display minimal or delayed mandibular growth, airway and deglutition problems can continue for years. Further intervention and monitoring with polysomnography, airway endoscopy and clinical assessments are necessary throughout infancy and into adulthood (Sher, 1992; Cohen et al, 2017).

After infancy, the management of patients with PRS involves the monitoring of general growth and development by pediatric specialists. Normally, cognitive, motor and psychosocial development of children with PRS is similar to unaffected children. Therefore, any deviations from typical development should be investigated. A common developmental challenge however,
is speech, which is helped with early and consistent speech therapy. After palatal cleft repair, speech and language pathologists generally evaluate these children on a yearly basis for the development of speech and velopharyngeal insufficiency which may require additional surgical procedures (Cohen et al., 2017). Another complication of the palatal clefting that children with PRS experience is increased episodes of serous otitis media and subsequent hearing problems requiring additional surgeries (Glynn et al., 2011). A significant majority of children will require myringotomy and placement of ventilation tubes to minimize liquid build-up in the middle ear (Dhillon, 1988).

Aside from speech therapy and myringotomies, a patient with PRS receives regular evaluation of their facial growth by the orthodontist from childhood into late adolescence. Primary concerns are the severity of the class II malocclusion due to the hypoplastic mandible, hypodontia as well as the possibility of damaged tooth buds after mandibular distraction therapy, if applicable (Evans et al., 2011; Cohen et al., 2017). Patients with PRS have a characteristic vertical craniofacial growth pattern along with hypoplasia of both, the maxilla and the mandible. In severe skeletal dysplasias and/or severe OSA situations, orthognathic surgery is required and is performed at skeletal maturity (Cohen et al., 2017). Based on what is known in the literature, the craniofacial growth pattern of patients with PRS is compared and contrasted to the growth pattern of patients with ICP and unaffected children in Section 3.

2.2. Isolated Cleft Palate (ICP)

Clefting of the orofacial complex is one of the most commonly reported birth defects. Minor deviations in the developmental process or in the precise timing of the events involved, can lead to the disruptions and clefting (Ross and Johnston, 1972). Orofacial clefts can be broadly classified as syndromic or non-syndromic depending on the presence of major and/or minor anomalies. Although non-syndromic clefts do not involve major anomalies, they may be associated with two or fewer minor malformations of minimal functional or esthetic significance (Wyszynski, 2002). Anything more would suggest the association of the cleft with a syndrome (Tolarova and Cervenka, 1998). Clefts are also further classified based on the tissues involved –
lip and/or alveolar process with or without palate and palate alone (Ross and Johnston, 1972). Isolated cleft palate is the rarest form of orofacial clefting and can be associated with other anomalies or syndromes about 50% of the time (Kirschner and LaRossa, 2000; Vieira, 2008; Burg et al, 2016). The most common syndrome associated with cleft palate is 22q11.2 deletion syndrome caused by deletion of a small segment of the long arm of chromosome 22. Other associated syndromes include Fetal Alcohol Syndrome, Treacher Collins syndrome and Stickler Syndrome among others (Praveen and Barbara, 2007). For the purposes of this investigation, the focus is on isolated non-syndromic cleft palate.

2.2.1. Prevalence

The prevalence of orofacial clefting shows wide variability depending on geographic location, ethnic group and socioeconomic conditions. It has been reported to be as high as 1:500 live births in Asian and Native American populations, to 1:1,000 live births in Caucasian populations and, 1:2,500 live births in African populations (Christensen and Mitchell, 1996; Beaty et al, 2010). Among those presenting with orofacial clefting, isolated cleft palate accounts for 33% of the diagnoses, while the majority are diagnosed with cleft lip and palate (46%) (Hopper et al, 2007). The reported incidence of cleft palate varies from 1 in 2,000 to 1 in 2,500 live births (Natsume et al, 2000; Vieira, 2008).

Variability in prevalence is also influenced by gender. Females are 66% more likely to be diagnosed with isolated cleft palate than males (Kirschner and LaRossa, 2000; Stanier and Moore, 2004). As well, females have been shown to present with more severe clefting than males (Christensen and Mitchell, 1996). This difference has been attributed to a longer palatal closure process in females thus increasing the period of vulnerability to teratogens (Burdi and Faist, 1967).

2.2.2 Etiology and Embryopathogenesis

Isolated cleft palate is considered an etiologically heterogeneous condition since multiple genetic and environmental factors have been implicated in its development (Christensen and Mitchell, 1996). Mutations in genes encoding various transcription factors, growth factor receptors, extracellular matrix components, and cell surface adhesion molecules have been reported to
cause cleft palate (Wilkie and Morriss-Kay, 2001). Mutations in the MSX1 gene have been associated with non-syndromic isolated cleft palate (Smith et al, 2012). Aside from genetic factors, environmental teratogens such as tobacco, alcohol, anticonvulsants, and retinoic acid have been associated with orofacial clefting (Hopper et al, 2007).

Cleft palate can result from a defect or interruption during one of the three stages of palatal formation - palatal shelf outgrowth, elevation of the palatal shelves and, fusion of the palatal shelves (Kaartinen et al, 1995). This critical period for palatogenesis begins at the end of the 5th week and lasts until the 12th week of embryonic development (Kirschner and LaRossa, 2000). In normal palatogenesis, during the 6th week of gestation, two palatal shelf-like processes emerge from the maxillary prominences and grow vertically on either side of the tongue. In the 7th week, the palatal shelves start to elevate and move towards each other assuming a horizontal orientation. Fusion begins by the end of the 9th week starting at the incisive foramen and moving posteriorly until the formation of the uvula by the 12th week (Ferguson, 1988; Gorlin et al, 1990). Any disruptions occurring during this period can cause clefting in the palate. The severity of the cleft depends upon the point at which the disruption occurred in palatal development. Palatal clefting may involve soft palate only or both hard and soft palate (Smith et al, 2012).

2.2.3 Cleft palate repair

Cleft palate repair involves the use of nasal and oral mucoperiosteal flaps to achieve palatal closure and velopharyngeal competence with minimal impact on maxillary growth (Nierzwicki and Daifallah, 2015). A successful outcome is dependent on the timing and the technique involved in the repair (Kirschner and LaRossa, 2000). Establishing an optimal time for the surgery has been a matter of controversy throughout the literature. It is believed that while early palatal repair benefits speech development, it may restrict midfacial growth. Dorf and Curtain (1982), demonstrated that palatal repair done before 12 months of age allows for significantly better speech articulation. Randall et al (1983) went further and specified that the age range at which palatal repair would provide the most speech benefit was 3-7 months. However, a recent study by Luyten et al (2014), found no significant differences in speech articulation and resonance characteristics in children who had palatal repair before 6 months of age (mean age - 3 months) and those that had the repair after 6 months of age (mean age - 11.1 months). Friede and
Pruzansky (1972) investigated effects of surgery on maxillary growth and demonstrated that as long as the surgical intervention did not utilize primary bone grafting procedures, palatal closure did not interfere with growth. However, restricted maxillary growth following surgical repair has been documented in the literature (Liao et al., 2002; Lu et al., 2007). Due to lack of conclusive evidence, the current recommendation is ‘before two years of age,’ more specifically 18 months of age, and is based on expert opinion (Follmar et al., 2015).

Currently, there is no consensus on the best surgical technique or protocol for cleft palate repair. Originally it was thought that since the Von Langenbeck technique produces less denuded palatal bone than the push-back technique, it results in less restriction of maxillary growth especially in the transverse dimension (Palmer et al., 1969). Jonsson and Thilander (1979) demonstrated a reduction in frequency of crossbite occlusion after using Von Langenbeck technique for their palatal closures. Several reports have shown that push-back technique has a significant influence on the shape of the maxilla causing reduction in the maxillary width and dental arches, with more severe restriction occurring in more severe cleft cases (Nystrom and Ranta, 1994; Heliovaara et al., 1993). Animal experimentation conducted by Leenstra et al. (1995) also supported the observation that keeping denuded palatal bony surfaces to a minimum reduces the negative impact of palatal repair on maxillary growth. Additionally, the areas denuded at palatal surgery should be kept as medial as possible to minimize the inhibitory effects of the post-surgical scar tissue formation (Ishikawa et al., 1998).

2.3. Effects on Craniofacial Growth

Growth of the mandible in patients with PRS has been a topic of controversy for many years. The major area of disagreement is whether or not “catch up” mandibular growth occurs in these patients after birth. Variable findings have been reported in the literature because most studies consist of small sample sizes, variable methodology and fail to separate subjects with syndromic and non-syndromic PRS. Rogers et al. in 2009 reported that mandibular morphology and position varies depending on whether PRS is associated with a syndrome or is occurring as an isolated entity. Therefore, combining syndromic and non-syndromic PRS in a study sample can
also lead to inaccuracies in the results. A summary of the literature review pertaining to catch up mandibular growth is presented in Table 1.

Aside from differences in growth of the mandible, the growth pattern of the maxilla and cranial base are also noted to be different when compared to unaffected children. Maxillary retraction has been consistently found in subjects with PRS which could be attributed to scar tissue formation after surgical cleft palate repair or due to intrinsic growth deficiency of a clefted maxilla. Bishara (1973) examined 20 Caucasian females with isolated cleft palate where 12 were operated and 8 were obturated. When compared to 32 unaffected Caucasian females, he found that the cleft group had smaller, posteriorly positioned maxillas and posteriorly positioned mandibles. The operated and unoperated cleft subgroups had no significant differences in maxillary and mandibular morphology, thus suggesting that surgical repair of the cleft may not be the only reason for altered craniofacial growth.

A summary of the findings in the literature are presented in Table 2 and in the following sections where craniofacial growth in patients with PRS is compared to patients with isolated cleft and normal control growth values.

2.3.1. Pierre Robin Sequence compared to Isolated Cleft Palate
Craniofacial morphology and pattern of growth for patients diagnosed with PRS and ICP are different in many ways to normal growth but similar in many ways to each other. Hermann et al (2003) compared craniofacial characteristics of 7 Danish children diagnosed with PRS to 53 Danish children diagnosed with ICP between the ages of 2 months to 22 months. They concluded that PRS had shorter posterior cranial bases, smaller mandibles in terms of length but similar in terms of height and width, and an increased mandibular plane angle although the gonial angles were similar. When comparing growth patterns, they found that the maxilla did not grow to the same extent in PRS children as it did in ICP children and the PRS group also tended to have a more vertical pattern of growth. Laitinen and Ranta (1991) compared 35 children diagnosed with non-syndromic PRS to 30 children diagnosed with ICP at approximately 9 years of age. Consistent with the previous study, at this age as well, the PRS group was found to have a slightly smaller maxilla with a steeper palatal plane, and a much smaller mandible with similar
gonial angles compared to the ICP group. In a mixed longitudinal study, Daskalogiannakis \textit{et al} (2001) compared 96 children with non-syndromic PRS to 50 children with ICP of various racial backgrounds at the approximate ages of 5.5 years. Of the 96 children with PRS, 38 of them were compared with the same 50 ICP children at the approximate ages of 10.5 years and 16.9 years. They found that throughout the 3 time points, mandibular length remained deficient in the PRS group. Although the differences in maxillary measurements (SNA and Ba-N-ANS) were not significant between the two groups, the midface depth (Ba-ANS) was shorter in the PR group. As well, consistent with the aforementioned studies, palatal plane and mandibular plane were steeper in the PRS group.

Evaluating growth and craniofacial form beyond 16 years of age, Laitinen \textit{et al} (1997) compared 30 Finnish young adults with non-syndromic PRS to 116 Finnish young adults with ICP of approximately 17 years and older. Similarities to the aforementioned studies were found along with the observation that the PRS group had shorter ramal length compared to the ICP group.

\textbf{2.3.2. Pierre Robin Sequence and Isolated cleft palate compared to Normal}

Figueroa \textit{et al} (1991) analyzed mandibular size during the first 2 years of life (3 months to 2 years) in 17 children with non-syndromic PRS, 26 children with ICP and 26 unaffected children. They found that the greatest difference in mandibular length between the groups was at the earliest time point. This difference reduced over time owing to a spike in mandibular growth rate in the PRS infants during the early months of life. Over the two years, although mandibular length increased by 53\% in the PRS group compared to 42\% for ICP and 38\% in the normal group, this was not enough to eliminate the differences seen in lengths, indicating only a partial catch-up in mandibular growth. PRS mandibles remained the smallest, followed by ICP and then normal mandibles. Shen \textit{et al} (2012) compared 13 children diagnosed with non-syndromic PRS to 14 children with ICP and normative cephalometric values measured at approximately 5 years of age and 12 years of age. Their comparison involving PRS to ICP was similar to other literature findings reported in the section above. Comparing PRS to normal values, they concluded that cranial base length, mandibular length and maxillary length were deficient at both time points. The mandible was also found to have a steeper mandibular plane angle. They also compared ICP to normal and found that although mandibular length in children with ICP started
out much smaller than normal at 5 years, at 12 years the lengths became almost similar (ICP still remained slightly shorter but not significantly shorter than normal). The maxillary length however, remained shorter than normal at both ages leading to sagittal jaw discrepancies as evidenced by negative ANB values.

Craniofacial characteristics of subjects with PRS in their adolescent years were investigated by Suri et al in 2010a. They compared 34 Caucasian children with non-syndromic PRS with age- and sex-matched unaffected controls at approximately 12 years and 16 years of age. They found that, in addition to deficiencies in cranial base, maxillary and mandibular lengths, subjects with PRS had steeper palatal planes, vertical pattern of growth and bimaxillary retrognathism. More specifically within the mandible, deficiencies were found in the mandibular body length and height, ramal length and width and anterior basal thickness.
**Table 1. Summary of the Literature: Catch-up mandibular growth in patients with PRS (Suri, 2014)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>PRS Sample size</th>
<th>Comparison Group</th>
<th>Catch up growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruzansky and Richmond - 1954</td>
<td>Case report</td>
<td>N - 3 (2mo – 4y)</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Beers and Pruzansky - 1955</td>
<td>Case report</td>
<td>N - 1 (10d – 15mo)</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Randall <em>et al</em> - 1965</td>
<td>Longitudinal case series</td>
<td>N - 22 (birth) N - 18 (1y)</td>
<td>None</td>
<td>1/3 caught up by year 1 1/2 improved with later growth</td>
</tr>
<tr>
<td>Randall <em>et al</em> - 1965</td>
<td>Case report</td>
<td>N - 2</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Hotz and Gnoinski - 1982</td>
<td>Cross sectional</td>
<td>N - 7 (5y)</td>
<td>ICP - 7</td>
<td>No</td>
</tr>
<tr>
<td>Figueroa <em>et al</em> – 1991</td>
<td>Longitudinal</td>
<td>N - 17 (3mo – 21.5mo)</td>
<td>ICP: N - 26 Normal: N - 26</td>
<td>Increased rate of growth in PRS mandibles - Partial catch-up</td>
</tr>
<tr>
<td>Vegter <em>et al</em> – 1999</td>
<td>Longitudinal case series</td>
<td>N - 7 (2mo – 22mo)</td>
<td>Normal: N - 100 (0mo) 42 (6mo) 32 (1y)</td>
<td>No</td>
</tr>
<tr>
<td>Daskalogiannakis <em>et al</em> – 2001</td>
<td>Retrospective longitudinal</td>
<td>N - 96 (5.5y) 38 (10.3y) 38 (16.8y)</td>
<td>ICP: N - 50 (5.5y) 50 (10.5y) 50 (17y)</td>
<td>No</td>
</tr>
<tr>
<td>Herman <em>et al</em> – 2003</td>
<td>Longitudinal</td>
<td>N - 7 (2mo – 22mo)</td>
<td>ICP: N - 53 (2mo – 22mo) UCLP: N - 48 (2mo – 22mo)</td>
<td>No</td>
</tr>
<tr>
<td>Matsuda <em>et al</em> – 2006</td>
<td>Case series</td>
<td>N - 5</td>
<td>None</td>
<td>Yes. Improved growth with treatment during adolescence</td>
</tr>
<tr>
<td>Ericson <em>et al</em> – 2006</td>
<td>Longitudinal</td>
<td>N - 7 (2mo – 22mo)</td>
<td>ICP: N - 66</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 2. Summary of the Literature: Craniofacial growth characteristics in patients with PRS and ICP in comparison with normal samples

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Sample size</th>
<th>Comparison group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibasaki and Ross – 1967</td>
<td>Retrospective</td>
<td>Part I: ICP: N - 30 @ avg age 6yrs &lt;br&gt;Part II: ICP: N - 36 @ 6y, 9y, 12y, 15y</td>
<td>Part I: Normal: N - 30 @ 6y &lt;br&gt;Part II: Normal: N - 30 @ 6y, 9y, 12y, 15y</td>
<td>Part I: Normal mandibular length but chin posteriorly displaced, increased gonial angle and mandibular inclination, retruded maxillary incisors, increased lower face height and increased freeway space &lt;br&gt;Part II: retruded facial growth pattern</td>
</tr>
<tr>
<td>Figueroa et al – 1991</td>
<td>Retrospective longitudinal</td>
<td>PRS: N - 17 @ 0-2y &lt;br&gt;Normal: N - 26 @ 0-2y &lt;br&gt;ICP: N - 26 @ 0-2y</td>
<td></td>
<td>Craniofacial morphology differs between PRS, ICP and normal. More so between PRS and normal than ICP and normal. Rate of change/growth higher in PRS than ICP and N and inversely related to age. Change in airway dimension and tongue area: PRS&gt;ICP&gt;N &lt;br&gt;Lower hyoid position in PRS</td>
</tr>
<tr>
<td>Ranta and Laitinen - 1992</td>
<td>Longitudinal</td>
<td>PRS: N - 35 @ avg. age 9.1y and 13.3y &lt;br&gt;ICP: N - 30 age and sex matched @ avg. age 7.1y and 12.4y</td>
<td></td>
<td>PRS: smaller and more retrognathically positioned mandibles &lt;br&gt;Morphogenetically similar mandibular development to ICP</td>
</tr>
<tr>
<td>Daskalogianakis et al - 2001</td>
<td>Retrospective mixed longitudinal</td>
<td>PRS: N - 96 @ 5.5y, 38 @ 10.3y, 38 @ 16.8y &lt;br&gt;ICP: N - 50 @ 5.7yrs, 50 @ 10.6yrs, 50 @ 17yrs</td>
<td></td>
<td>PRS: retrognathic mandible, shorter mandibular length, steep mandibular plane, steep palatal plane. Dental: retroclined max incisors, proclined mandibular incisors, deep overbite and large overjet</td>
</tr>
<tr>
<td>Suri et al – 2010a</td>
<td>Retrospective longitudinal</td>
<td>PRS: N - 34 @ avg age 11.8 and 16.6 &lt;br&gt;Normal: N - 34 age, sex and ethnicity matched</td>
<td></td>
<td>PRS: Bimaxillary retrognathism, steep palatal plane, vertical growth pattern, reduced lengths of maxilla, cranial base and mandible, and large gonial angles</td>
</tr>
<tr>
<td>Horsewell and Gallup – 1992</td>
<td>Retrospective longitudinal</td>
<td>ICP + UCLP + BCLP + CL/A: N - 542 @ ages 7y-18y</td>
<td>Normal: N - 277 @ ages 7y-18y</td>
<td>ICP: Anterior cranial base length was smaller than Normal &lt;br&gt;As well posterior cranial base length shorter from 12-18. Acute cranial base angle – signifies nasopharynx deficiency and midface retrusion</td>
</tr>
<tr>
<td>daSilva, Normando and Capelozzo – 1992</td>
<td>Retrospective</td>
<td>ICP: N - 43 operated cases</td>
<td>ICP: N - 43 non-operated cases</td>
<td>ICP: no significant difference between operated and unoperated cases in terms of mandibular length and spatial position</td>
</tr>
</tbody>
</table>
3. Purpose of the study, Research Objective and Hypothesis

3.1. Purpose of the study

The purposes of this retrospective longitudinal study are:

- To characterize the differences in craniofacial morphology and growth in patients with PRS and unaffected children from childhood to late adolescence
- To characterize the differences in craniofacial morphology and growth in patients with PRS and patients with ICP from childhood to late adolescence
3.2. Research Objectives

The objectives of this study are:

- To longitudinally evaluate craniofacial growth and identify morphological differences in the maxilla, mandible and cranial base of patients with non-syndromic PRS in comparison to patients with isolated cleft palate at 3 time points: 6 years, 12 years and 18 years.

- To longitudinally evaluate craniofacial growth and identify morphological differences in the maxilla, mandible and cranial base of patients with PRS in comparison to unaffected subjects with class I skeletal growth patterns and occlusions at 3 time points: 6 years, 12 years and 18 years.
3.3. Hypotheses

To address the research objectives, the following null hypotheses were formulated:

**Null hypothesis 1:**

There are no significant differences in craniofacial morphology and growth patterns of patients with non-syndromic PRS in comparison to unaffected children.

**Null hypothesis 2:**

There are no significant differences in craniofacial morphology and growth patterns of patients with non-syndromic PRS in comparison to patients with isolated cleft palate.
4. Materials and Methods

This retrospective longitudinal cephalometric study was approved by the Hospital for Sick Children’s Research Ethics Board as well as the University of Toronto Research Ethics Board.

The plan for the study was to assess longitudinal craniofacial growth in the same patient from the age of 6 years to 18 years. For this purpose, three time points were selected to approximate prepubertal and pubertal growth phases, as well as the end of the active facial growth phase:

- T1 or average age of 6 years, the beginning of the transitional dentition period and before any orthodontic interventions
- T2 or average age of 12 years, when the patient entered the permanent dentition stage of dental development and before any orthodontic interventions.
- T3 or average age of 18 years, when the patient reaches adulthood, after completion of orthodontic treatment but before orthognathic surgery.

4.1. Sample Description

4.1.1. Pierre Robin Sequence group:

The Hospital for Sick Children (HSC) receives approximately 7-18 patients per year of various racial backgrounds, who are diagnosed with Pierre Robin Sequence. These children are either born at the hospital itself or sent from other birth centres across the province of Ontario. The diagnosis of PRS at HSC is based on the following criteria:

- Presence of mandibular micrognathia
- Cleft palate
- At least 1 episode of respiratory distress in the neonatal period

Patients with PRS are under the care of a multi-disciplinary team which involves regular orthodontic evaluations at the HSC orthodontic clinic. As part of this evaluation, they receive lateral cephalometric imaging and panoramic imaging at regular intervals to evaluate growth and plan for future orthodontic treatment.
The inclusion criteria for the PRS group were:

- Caucasian descent – in order to maintain racial homogeneity and eliminate variations introduced by race-specific craniofacial features.
- Diagnosis of non-syndromic PRS - Mandibular size, morphology, and position are significantly variable in children with a syndromic PRS (Rogers et al, 2009). Hence, separating syndromic and non-syndromic PRS is important to maintain homogeneity and reduce variations in the study sample.
- Have lateral cephalometric radiographs at approximately 6 years, 12 years and 18 years since these were the time points selected for the study.

After applying the inclusion criteria to patients diagnosed with PRS at HSC, the final PRS study group included patients who were born between 1954 and 1991. A total of 43 patients consisting of 18 males and 25 females were selected and their mean ages at each time point are summarized in Table 3. These patients had surgical cleft palate repair at a mean age of 17.7 months (± 1.8 months) using Von Langenbeck or push-back palatoplasty techniques.

Lateral cephalometric images had been acquired using standard equipment and methodology adhering to the protocols of the hospital. These images were imported into the Dolphin Imaging software (version 11.8.06.24 Premium; Patterson Dental Supply Inc., Richmond, WA) for the purposes of cephalometric tracing and analysis.

<table>
<thead>
<tr>
<th>Time point</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>6y5m (range: 5y2m - 7y8m)</td>
<td>6y (range: 5y - 8y3m)</td>
</tr>
<tr>
<td>T2</td>
<td>11y8m (range: 9y2m - 13y10m)</td>
<td>12y3m (range: 9y2m - 13y7m)</td>
</tr>
<tr>
<td>T3</td>
<td>16y5m (range: 14y11m - 19y9m)</td>
<td>16y10m (range: 14y - 18y11m)</td>
</tr>
</tbody>
</table>

4.1.2. **Isolated Cleft Palate group – control group**

As part of their treatment, patients with ICP receive regular orthodontic evaluations at the HSC orthodontic clinic. Lateral cephalometric imaging and panoramic imaging are taken at regular intervals to evaluate growth of the jaws and need for orthodontic treatment and future orthognathic surgery.
After applying the same inclusion criteria used for the PRS group, a total of 43 patients consisting of 18 males and 25 females were selected such that their lateral cephalometric radiographs had been taken at ages that closely matched the PRS sample. The final non-syndromic ICP group consisted of patients born between 1949 and 1980. Table 4 summarizes the mean ages of the ICP group at each of the three time points. These patients had surgical palatal repair at a mean age of 20.4 months (+/- 7.1 months) using Von Langenbeck or push-back palatoplasty techniques.

Lateral cephalometric images were then imported into the Dolphin Imaging software (version 11.8.06.24 Premium; Patterson Dental Supply Inc., Richmond, WA) for the purposes of cephalometric tracing and analysis.

**Table 4. Mean ages: Isolated Cleft Palate group**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>6y8m (range: 5y1m - 7y10m)</td>
<td>6y8m (range: 5y4m – 7y11m)</td>
</tr>
<tr>
<td>T2</td>
<td>12y10m (range: 9y6m – 13y5m)</td>
<td>12y1m (range: 9y7m – 13y10m)</td>
</tr>
<tr>
<td>T3</td>
<td>17y1m (range: 14y4m – 19y6m)</td>
<td>16y10m (range: 14y7m - 21y)</td>
</tr>
</tbody>
</table>

**4.1.3. Unaffected children – control group:**

The Burlington Growth Centre (BGC) study is a collection of longitudinal craniofacial growth records of a predominantly Caucasian, and mostly Anglo-Saxon, group of individuals that made up the local population at that time. An original sample of 1258 children representing 90% of the Burlington children, were separated into 5 study groups:

- Serial experimental group at age 3 (SE) (N – 312): Records taken annually from age 3-20
- Serial control at age 6 (C-6) (N: 295): Records taken at ages 6, 9, 12, 14, 16 and 20
- Serial control at age 8 (C-8) (N: 219): Records taken at age 8
- Serial control at age 10 (C-10) (N: 217): Records taken at age 10
- Serial control at age 12 (C-12) (N: 215): Records taken at age 12

For the current investigation, 18 male and 25 female children were selected from the SE and C-6 groups who had lateral cephalometric images taken at ages that closely matched the sample of
non-syndromic PRS. As well, to be selected, the subject’s growth pattern and occlusion should have been recorded in the archives as class I. The mean ages of the final control group of unaffected children is presented in Table 5. The digital lateral cephalometric images taken in centric occlusion, were then imported into the Dolphin Imaging software (version 11.8.06.24 Premium; Patterson Dental Supply Inc., Richmond, WA) for the purposes of cephalometric tracing and analysis.

**Table 5. Mean Ages: Unaffected Group**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>6y4m (range: 5y-7y)</td>
<td>6y5m (range: 5y-8y)</td>
</tr>
<tr>
<td>T2</td>
<td>11y7m (range: 9y-14y)</td>
<td>12y (range: 9y-14y)</td>
</tr>
<tr>
<td>T3</td>
<td>16y5m (range: 15y-19y)</td>
<td>16y10m (range: 14y-18y)</td>
</tr>
</tbody>
</table>

**4.2. Cephalometric Analysis**

Using Dolphin Imaging software, lateral cephalometric records were analyzed using a custom cephalometric analysis previously described by Suri et al (2006, 2010b). This consisted of measurements from conventional analyses, as well as, additional landmarks and measurements to study regional detail of the maxilla, mandible and cranial base. Figure 1 illustrates the unique cephalometric landmarks involved in this analysis. Landmark and measurement descriptions are summarized in Table 6 and Table 7. In order to maintain consistency, a single technician traced and digitized all radiographs in the manner presented in Figure 2.
Figure 1. Illustration of a lateral cephalogram labelled with the custom landmarks (Suri et al., 2010b)

Figure 2. A digitized lateral cephalogram
<table>
<thead>
<tr>
<th>Landmark</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba (Basion)</td>
<td>Most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen</td>
</tr>
<tr>
<td>Na (Nasion)</td>
<td>Intersection of the internasal suture with the nasofrontal suture in the midsaggittal plane</td>
</tr>
<tr>
<td>S (Sella)</td>
<td>Center of the pituitary fossa of the sphenoid bone</td>
</tr>
<tr>
<td>Po (Porion)</td>
<td>Highest point of the external auditory meatus</td>
</tr>
<tr>
<td>O (Orbitale)</td>
<td>Lowest point of the external border of the orbital cavity</td>
</tr>
<tr>
<td>ANS (Anterior Nasal Spine)</td>
<td>The tip of the anterior nasal spine</td>
</tr>
<tr>
<td>PNS (Posterior Nasal Spine)</td>
<td>Tip of the posterior nasal spine</td>
</tr>
<tr>
<td>Sn</td>
<td>Most posterior midline point on the premaxilla between the anterior nasal spine and prosthion</td>
</tr>
<tr>
<td>A (A point)</td>
<td>A point – Deepest point of the curve of the maxilla between the ANS and dental alveolus</td>
</tr>
<tr>
<td>Pr (Prosthion)</td>
<td>Most anterior and inferior point on the alveolar process between the maxillary central incisors</td>
</tr>
<tr>
<td>Co (Condylion)</td>
<td>The most posterior superior point of the condyle</td>
</tr>
<tr>
<td>Go (Gonion)</td>
<td>Most convex point along the inferior border of the ramus</td>
</tr>
<tr>
<td>Me (Menton)</td>
<td>Most inferior point of the symphysis</td>
</tr>
<tr>
<td>Gn (Gnathion)</td>
<td>Midpoint between the most anterior and inferior point on the bony chin</td>
</tr>
<tr>
<td>B (B point)</td>
<td>Most posterior point in the concavity along the anterior border of the symphysis</td>
</tr>
<tr>
<td>Pg (Pogonion)</td>
<td>Most anterior point on the mid-sagittal symphysis</td>
</tr>
<tr>
<td>Id (Infradentale)</td>
<td>Most superior and anterior point on the alveolar process in between the mandibular central incisors</td>
</tr>
<tr>
<td>Idl (Lingual infradentale)</td>
<td>Directly opposite Id on the lingual surface</td>
</tr>
<tr>
<td>Prl (Lingual prosthion)</td>
<td>Directly opposite Pr on the lingual surface</td>
</tr>
<tr>
<td>Al (Lingual A point)</td>
<td>Directly opposite A point on the lingual surface</td>
</tr>
<tr>
<td>Pamaxj (palate-anterior maxillary junction)</td>
<td>Most superoanterior point on palatal contour of basal anterior maxilla</td>
</tr>
<tr>
<td>Mamax (midpoint of anterior maxillary base)</td>
<td>Midpoint of line drawn from pamaxj to Sn</td>
</tr>
<tr>
<td>Amaxaj (anterior maxilla-alveolar junction)</td>
<td>Midpoint of line drawn from Al to A</td>
</tr>
<tr>
<td>Malvmx (midpoint of anterior alveolus, maxillary)</td>
<td>Midpoint of line drawn from Prl to Pr</td>
</tr>
<tr>
<td>PAPmd (posterior alveolar point, mandibular)</td>
<td>Most posteroinferior mid planed point on the anterior border of the ascending ramus</td>
</tr>
<tr>
<td>Inf Go (inferior gonion)</td>
<td>Mid planed point on the lower border of the mandible where the convexity at gonion merges with the concavity of the antegonial notch</td>
</tr>
<tr>
<td>RBS (ramus body syncline)</td>
<td>Point of intersection of a line drawn from Inf Go to PAPmd with the cortical outline of the mid planed mandibular nerve</td>
</tr>
<tr>
<td>BI (Lingual point B)</td>
<td>Point of intersection of a line drawn from RBS to B with the lingual contour of the symphysis</td>
</tr>
<tr>
<td>Saj (symphysis alveolar junction)</td>
<td>Midpoint of a line drawn from BI to B</td>
</tr>
<tr>
<td>Pgl (lingual point pogonion)</td>
<td>Most prominent point on the lingual contour of the symphysis, as located by the greatest perpendicular distance from a line drawn from Saj to Me</td>
</tr>
<tr>
<td>Malvmmd (midpoint of anterior alveolus, mandibular)</td>
<td>Midpoint of line drawn from Id(l) to Id</td>
</tr>
</tbody>
</table>
Table 7. Cephalometric Analysis: Definitions of the linear and angular measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cranial base length</td>
<td>Length of line drawn from S to N</td>
</tr>
<tr>
<td>Cranial base angle</td>
<td>Internal angle Ba-S-Na</td>
</tr>
<tr>
<td>Maxillary length</td>
<td>Length of line drawn from ANS to PNS</td>
</tr>
<tr>
<td>Maxillary anterior basal width</td>
<td>Length of line drawn from pamaxj to Sn</td>
</tr>
<tr>
<td>Maxillary anterior apical width</td>
<td>Length of line drawn from Al to A</td>
</tr>
<tr>
<td>Anterior maxillary height</td>
<td>Length of perpendicular dropped from amaxaj to PNS-ANS</td>
</tr>
<tr>
<td>Maxillary anterior alveolar height</td>
<td>Length of line drawn from amaxaj to malvmx</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection</td>
<td>Internal angle between the palatal plane (ANS-PNS) and line drawn from amaxaj to mamax</td>
</tr>
<tr>
<td>Mandibular length</td>
<td>Length of line drawn from Co to Gn</td>
</tr>
<tr>
<td>External ramal length</td>
<td>Length of line drawn from Co to Go</td>
</tr>
<tr>
<td>Internal ramal length</td>
<td>Length of line drawn from Co to RBS</td>
</tr>
<tr>
<td>External body length</td>
<td>Length of line drawn from Go to Gn</td>
</tr>
<tr>
<td>Internal body length</td>
<td>Length of line drawn from RBS to Gn</td>
</tr>
<tr>
<td>Gonial angle</td>
<td>Internal angle Co-Go-Gn</td>
</tr>
<tr>
<td>Internal mandibular deflection</td>
<td>Internal angle Co-RBS-Gn</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height</td>
<td>Length of the perpendicular dropped from PAPmd to RBS-B</td>
</tr>
<tr>
<td>Mandibular posterior body height</td>
<td>Length of the perpendicular dropped from Inf Go to RBS-B</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height</td>
<td>Length of the line drawn from malvmd to saj</td>
</tr>
<tr>
<td>Symphyseal height</td>
<td>Length of line drawn from saj to Me</td>
</tr>
<tr>
<td>Symphyseal thickness</td>
<td>Sum of the lengths of perpendiculars dropped from Pg and Pgl to a line drawn from saj to Me</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection</td>
<td>Internal angle between Go-Gn and the line drawn from saj to Me</td>
</tr>
<tr>
<td>Ramal width</td>
<td>Length of the line drawn from the mid planed deepest points on the posterior and anterior borders of the ramus</td>
</tr>
<tr>
<td>Mandibular anterior apical base width</td>
<td>Length of the line drawn from BI to B</td>
</tr>
<tr>
<td>ANB angle</td>
<td>Difference between SNA and SNB angles indicating the skeletal relationship between the maxilla and the mandible</td>
</tr>
</tbody>
</table>

4.3. Statistics

Statistical analysis of the data was completed using the Statistical Package for the Social Sciences software (IBM SPSS v. 20; SPSS Inc., Chicago, IL.). Pairwise comparisons were conducted using Tukey’s correction adjusted for gender effects. Longitudinal comparisons across all time points were made using linear mixed models adjusted for age and gender effects. Measurements with p-values of less than 0.05 were reported as statistically significant.
4.4. Reliability Analysis

To assess intraexaminer repeatability of the cephalometric method, 5 patients from each group were randomly selected. Their radiographs at all three time points were retraced and redigitized 3 months after the initial digitization was completed. Repeatability was assessed through linear and angular measurements recorded at both times and correlated by the intraclass correlation coefficient analysis. Table 8 summarizes the results of the repeatability assessment and shows a highly significant agreement between the measurements recorded at the initial tracing phase and the repeated tracing phase. This demonstrates excellent repeatability of the cephalometric method used in this study.

Table 8. Intraexaminer repeatability of cephalometric measurements of 15 randomly selected subjects.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Trial 1</th>
<th></th>
<th>Trial 2</th>
<th></th>
<th>ICCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Cranial Base</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial base angle (°)</td>
<td>130.55</td>
<td>5.4</td>
<td>130.32</td>
<td>5.33</td>
<td>0.96</td>
</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>69.23</td>
<td>4.45</td>
<td>69.03</td>
<td>4.49</td>
<td>0.99</td>
</tr>
<tr>
<td>Maxilla</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>48.11</td>
<td>5.35</td>
<td>48.85</td>
<td>5.05</td>
<td>0.95</td>
</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>17.78</td>
<td>2.78</td>
<td>17.68</td>
<td>2.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Maxillary anterior apical width (mm)</td>
<td>11.42</td>
<td>1.88</td>
<td>11.31</td>
<td>1.82</td>
<td>0.89</td>
</tr>
<tr>
<td>Anterior maxillary height (mm)</td>
<td>7.92</td>
<td>1.63</td>
<td>8.02</td>
<td>1.69</td>
<td>0.9</td>
</tr>
<tr>
<td>Maxillary anterior alveolar height (mm)</td>
<td>17.42</td>
<td>2.43</td>
<td>17.71</td>
<td>2.49</td>
<td>0.95</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection (°)</td>
<td>146.64</td>
<td>14.3</td>
<td>145.69</td>
<td>13.72</td>
<td>0.95</td>
</tr>
<tr>
<td>Mandible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal mandibular deflection (°)</td>
<td>148.79</td>
<td>7.79</td>
<td>147.42</td>
<td>6.86</td>
<td>0.95</td>
</tr>
<tr>
<td>Condylion - Gonion - Anatomical Gnathion (°)</td>
<td>122.18</td>
<td>7.36</td>
<td>121.71</td>
<td>6.06</td>
<td>0.96</td>
</tr>
<tr>
<td>Mandibular length (Co-Gn)(mm)</td>
<td>108.84</td>
<td>12.08</td>
<td>108.53</td>
<td>12.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Internal body length (mm)</td>
<td>54.74</td>
<td>8.02</td>
<td>54.9</td>
<td>8.06</td>
<td>0.98</td>
</tr>
<tr>
<td>Co-Go (mm)</td>
<td>54.11</td>
<td>7.66</td>
<td>53.9</td>
<td>7.78</td>
<td>0.98</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>58.43</td>
<td>6.72</td>
<td>58.45</td>
<td>6.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Ramal width (mm)</td>
<td>30.35</td>
<td>2.98</td>
<td>30.27</td>
<td>2.83</td>
<td>0.95</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height (mm)</td>
<td>15.06</td>
<td>2.9</td>
<td>15.65</td>
<td>3.24</td>
<td>0.91</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>9.19</td>
<td>2.51</td>
<td>8.56</td>
<td>2.08</td>
<td>0.84</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>11.83</td>
<td>2.2</td>
<td>11.79</td>
<td>2.39</td>
<td>0.91</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>8.27</td>
<td>1.49</td>
<td>8.48</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Symphyseal height (mm)</td>
<td>20.76</td>
<td>2.84</td>
<td>20.75</td>
<td>2.94</td>
<td>0.93</td>
</tr>
<tr>
<td>Symphyseal thickness (mm)</td>
<td>13.38</td>
<td>2.17</td>
<td>13.33</td>
<td>2.16</td>
<td>0.94</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection (°)</td>
<td>72.93</td>
<td>7.17</td>
<td>73</td>
<td>7.58</td>
<td>0.97</td>
</tr>
</tbody>
</table>
5. Results

Following digitization of all radiographs, an averaged tracing for each group at each time point was created. These tracings were superimposed on each other for comparison of craniofacial growth patterns at each time point (Figures 3, 4, and 5). As well, the averaged tracings of each group at the three time points were superimposed on each other, to visually appreciate the growth patterns within the group (Figures 6, 7, and 8). Across the three time points, the growth patterns of the PRS group and the ICP group were similar to each other, however, they were quite different from the unaffected group. For overall comparison of craniofacial growth, the tracings were superimposed on anterior cranial base, registered at Sella. The maxilla and mandible of the PRS and ICP groups appear to be retrognathic when compared to the unaffected group. The length of the mandible appears to be most deficient in the PRS group, followed by the ICP group and then the unaffected group. This is also confirmed from the mandibular superimpositions of the three groups at each time point, which was done by overlaying the tracings on the lingual outline of the symphysis. The PRS group also appeared to have the most vertical pattern of growth compared to the other two groups. Anterior cranial bases were indifferent between the three groups. For comparison of the maxilla, the tracings were superimposed on the palatal plane, registered at ANS. It can be noted that the maxillary length of the PRS and ICP groups were similar to each other but shorter when compared to the unaffected group.
Figure 3. Superimposition of averaged tracings of PRS, ICP and normal groups at T1.

Figure 4. Superimposition of averaged tracings of PRS, ICP and normal groups at T2.

Figure 5. Superimposition of averaged tracings of PRS, ICP and normal groups at T3.
Figure 6. Superimposition of averaged tracings of the PRS group at T1, T2 and T3

Figure 7. Superimposition of averaged tracings of the ICP group at T1, T2 and T3
Figure 8. Superimposition of averaged tracings of the normal group at T1, T2 and T3
For each group, the mean values (with and without adjustment for gender) of each cephalometric measurement at each time point are presented in Tables 9, 10 and 11. Results of the pairwise comparisons using Tukey’s correction with adjustments for gender are presented in Tables 12, 13, and 14. Comparisons across time were conducted using linear mixed models with adjustments for age and gender effects and are summarized in Tables 15, 16, and 17.

Table 9. Mean values with and without adjustment for gender of the cephalometric measurements at T1.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>T1</th>
<th>Normal</th>
<th>ICP</th>
<th>PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>STD</td>
<td>Adj Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>Cranial Base</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial base angle (o)</td>
<td>130.335</td>
<td>4.374</td>
<td>130.231</td>
<td>129.819</td>
</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>67.488</td>
<td>2.504</td>
<td>67.769</td>
<td>66.73</td>
</tr>
<tr>
<td>Maxilla</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>46.805</td>
<td>2.793</td>
<td>46.949</td>
<td>42.87</td>
</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>16.974</td>
<td>2.002</td>
<td>17.079</td>
<td>16.114</td>
</tr>
<tr>
<td>Anterior maxillary height (mm)</td>
<td>7.205</td>
<td>1.023</td>
<td>7.222</td>
<td>6.735</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection (o)</td>
<td>144.009</td>
<td>9.544</td>
<td>144.108</td>
<td>143.428</td>
</tr>
<tr>
<td>Mandible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal mandibular deflection (o)</td>
<td>152.019</td>
<td>5.414</td>
<td>151.996</td>
<td>154.523</td>
</tr>
<tr>
<td>Mandibular length (Co-Gn)(mm)</td>
<td>100.656</td>
<td>4.183</td>
<td>100.961</td>
<td>96.891</td>
</tr>
<tr>
<td>Internal body length (mm)</td>
<td>50.028</td>
<td>3.098</td>
<td>50.09</td>
<td>48.074</td>
</tr>
<tr>
<td>Co-Go (mm)</td>
<td>48.056</td>
<td>3.207</td>
<td>48.146</td>
<td>45.107</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>53.853</td>
<td>2.999</td>
<td>54.098</td>
<td>51.395</td>
</tr>
<tr>
<td>Ramal width (mm)</td>
<td>29.293</td>
<td>2.033</td>
<td>29.041</td>
<td>27.288</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height (mm)</td>
<td>12.074</td>
<td>1.616</td>
<td>12.149</td>
<td>13.04</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>8.567</td>
<td>1.458</td>
<td>8.549</td>
<td>6.747</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>10.149</td>
<td>1.921</td>
<td>10.149</td>
<td>9.677</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>8.667</td>
<td>1.536</td>
<td>8.715</td>
<td>7.733</td>
</tr>
<tr>
<td>Symphyseal height (mm)</td>
<td>18.458</td>
<td>1.829</td>
<td>18.493</td>
<td>18.595</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection (o)</td>
<td>78.279</td>
<td>5.657</td>
<td>78.235</td>
<td>76.8</td>
</tr>
</tbody>
</table>
### Table 10. Mean values with and without adjustment for gender of the cephalometric measurements at T2.

<table>
<thead>
<tr>
<th>T2</th>
<th>Normal</th>
<th>ICP</th>
<th>PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements</td>
<td>Mean</td>
<td>STD</td>
<td>Adj Mean</td>
</tr>
<tr>
<td>Cranial Base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial base angle (°)</td>
<td>129.821</td>
<td>4.562</td>
<td>129.717</td>
</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>72.005</td>
<td>3.081</td>
<td>72.285</td>
</tr>
<tr>
<td>Maxilla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>53.36</td>
<td>2.882</td>
<td>53.504</td>
</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>19.779</td>
<td>2.266</td>
<td>19.884</td>
</tr>
<tr>
<td>Anterior maxillary height (mm)</td>
<td>8.626</td>
<td>1.235</td>
<td>8.643</td>
</tr>
<tr>
<td>Maxillary anterior alveolar height (mm)</td>
<td>17.835</td>
<td>1.341</td>
<td>17.881</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection (°)</td>
<td>145.635</td>
<td>9.887</td>
<td>145.734</td>
</tr>
<tr>
<td>Mandible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condylion - Gonion - Anatomical Gnathion (°)</td>
<td>121.349</td>
<td>4.19</td>
<td>121.409</td>
</tr>
<tr>
<td>Mandibular length (Co-Gn)(mm)</td>
<td>114.014</td>
<td>5.335</td>
<td>114.319</td>
</tr>
<tr>
<td>Internal body length (mm)</td>
<td>59.005</td>
<td>3.84</td>
<td>59.066</td>
</tr>
<tr>
<td>Co-Go (mm)</td>
<td>54.844</td>
<td>4.694</td>
<td>55.134</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>59.458</td>
<td>3.85</td>
<td>59.703</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>10.686</td>
<td>1.891</td>
<td>10.667</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>11.56</td>
<td>1.587</td>
<td>11.605</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>9.093</td>
<td>1.321</td>
<td>9.141</td>
</tr>
<tr>
<td>Symphysial height (mm)</td>
<td>20.83</td>
<td>2.073</td>
<td>20.865</td>
</tr>
<tr>
<td>Mandibular plane/symphysial deflection (°)</td>
<td>73.9</td>
<td>5.563</td>
<td>73.856</td>
</tr>
</tbody>
</table>
Table 11. Mean values with and without adjustment for gender of the cephalometric measurements at T3.

<table>
<thead>
<tr>
<th></th>
<th>T3</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>12.793</td>
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<td>12.844</td>
<td>12.13</td>
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<td>152.116</td>
<td>9.78</td>
<td>152.215</td>
<td>152.977</td>
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<td>Co-Go (mm)</td>
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<td>Ramal width (mm)</td>
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<td>15.377</td>
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<td>Mandibular plane/symphyseal deflection (°)</td>
<td>72.028</td>
<td>5.686</td>
<td>71.984</td>
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<td>68.619</td>
<td>66.942</td>
<td>7.135</td>
<td>66.898</td>
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Table 12. Pairwise comparisons of mean measurements adjusted for gender using Tukey’s comparison at T1

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<tr>
<th>T1</th>
<th>PRS vs Normal</th>
<th>PRS vs ICP</th>
<th>ICP vs Normal</th>
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<td>Measurements</td>
<td>Mean(SE)</td>
<td>pvalue</td>
<td>Sig</td>
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<tr>
<td>Cranial Base</td>
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</tr>
<tr>
<td>Cranial base angle (°)</td>
<td>0.993 (1.134)</td>
<td>0.994</td>
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</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>-0.749 (0.750)</td>
<td>0.986</td>
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<tr>
<td>Maxilla</td>
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<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>-4.977 (0.704)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>-1.179 (0.433)</td>
<td>0.144</td>
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<td>Maxillary anterior apical width (mm)</td>
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<td>Anterior maxillary height (mm)</td>
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<td>Maxillary anterior alveolar height (mm)</td>
<td>-0.140 (0.392)</td>
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<td>Palatal/anterior maxillary deflection (°)</td>
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<td>Internal mandibular deflection (°)</td>
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<td>Condylion - Gonion - Anatomical Gnathion (°)</td>
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<td>Mandibular length (Co-Gn)(mm)</td>
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<tr>
<td>Internal body length (mm)</td>
<td>-6.486 (0.878)</td>
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<tr>
<td>Co-Go (mm)</td>
<td>-3.363 (1.036)</td>
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<td>Internal ramal length (mm)</td>
<td>-3.784 (0.860)</td>
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<td>Ramal width (mm)</td>
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<td>Mandibular posterior alveolar height (mm)</td>
<td>-0.042 (0.500)</td>
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<td>Mandibular posterior body height (mm)</td>
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<td>Mandibular anterior alveolar height (mm)</td>
<td>-0.121 (0.397)</td>
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<td>Mandibular anterior apical base width (mm)</td>
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<td>Symphyseal height (mm)</td>
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<td>Mandibular plane/symphyseal deflection (°)</td>
<td>3.260 (1.413)</td>
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Table 13. Pairwise comparisons of mean measurements adjusted for gender using Tukey’s comparison at T2.

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<td>Maxillary length (ANS-PNS) (mm)</td>
<td>Mandibular plane/symphyseal deflection (°)</td>
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<td>PRS vs Normal</td>
<td>1.281 (1.134)</td>
<td>-7.858 (0.704)</td>
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<td>0.012 (1.134)</td>
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<th>Anterior Cranial Base (SN) (mm)</th>
<th>Maxillary anterior apical width (mm)</th>
<th>Mandibular posterior body height (mm)</th>
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<th>Maxillary anterior basal width (mm)</th>
<th>Anterior maxillary height (mm)</th>
<th>Symphyseal height (mm)</th>
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<th>Mandibular posterior alveolar height (mm)</th>
<th>Mandibular anterior apical base width (mm)</th>
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<td>0.060 (0.397)</td>
<td>0.535 (0.500)</td>
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Table 14. Pairwise comparisons of mean measurements adjusted for gender using Tukey’s comparison at T3

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<td>Cranial Base</td>
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<td>Cranial base angle (°)</td>
<td>1.277 (1.134)</td>
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<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>-2.021 (0.750)</td>
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<td>Maxillary length (ANS-PNS) (mm)</td>
<td>7.774 (0.704)</td>
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<td>Maxillary anterior apical width (mm)</td>
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<td>0.165 (0.268)</td>
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<td>Maxillary anterior alveolar height (mm)</td>
<td>-1.109 (0.392)</td>
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<td>Palatal/anterior maxillary deflection (°)</td>
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<td>Mandible</td>
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<td>Internal mandibular deflection (°)</td>
<td>8.305 (1.222)</td>
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<td>Mandibular length (Co-Gn)(mm)</td>
<td>9.472 (1.303)</td>
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<td>Internal body length (mm)</td>
<td>8.165 (0.878)</td>
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</tr>
<tr>
<td>Co-Go (mm)</td>
<td>4.547 (1.036)</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>4.014 (0.860)</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Ramal width (mm)</td>
<td>2.819 (0.645)</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height (mm)</td>
<td>0.912 (0.500)</td>
<td>0.666</td>
<td>No</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>2.191 (0.394)</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>0.226 (0.397)</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>0.837 (0.291)</td>
<td>0.099</td>
<td>No</td>
</tr>
<tr>
<td>Symphyseal height (mm)</td>
<td>0.030 (0.491)</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Symphyseal thickness (mm)</td>
<td>1.784 (0.349)</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection (°)</td>
<td>5.086 (1.413)</td>
<td>0.011</td>
<td>Yes</td>
</tr>
</tbody>
</table>

5.1. PRS vs Normal:

Cranial base angle and anterior cranial base length were not significantly different at any of the three time points that were analyzed. Although, the difference in growth increment from T1 to T2 in the anterior cranial base length was statistically significant, the overall difference in growth increment was not statistically significant.

Maxillary length in the PRS group remained significantly smaller than the normal group at all three time points. Horizontal maxillary growth was significantly deficient between T1 and T2. The overall amount of growth in maxillary anterior basal width and maxillary anterior apical width were significantly smaller in the PRS group. All other maxillary measurements were similar between the two groups.
Mandibular length, symphyseal thickness and ramal length in the PRS group remained significantly smaller than the normal group at all three time points. The difference in ramal width, however, was only statistically significant at T1 and T3 with most of the deficiency in growth occurring between T2 and T3. Although the mandibular posterior body height was smaller in PRS subjects at T1, the difference was not statistically significant. This difference became significantly larger at T2 and T3 with overall statistically significant deficiency in growth increments in PRS subjects. PRS subjects displayed a vertical growth pattern with a significantly larger gonial angle and internal deflection angle at all three time points. Although the mandibular plane-symphyseal deflection was consistently smaller in the PRS group, it was only statistically significant at T3.

Table 15. Linear mixed model analysis of growth differences between PRS and Normal groups.
5.2. PRS vs ICP:

There were no significant differences in the cranial bases of the PRS and ICP groups. Maxillas of the PRS and ICP groups were similar in most aspects. Maxillary anterior alveolar height remained deficient in the PRS group at all three time points, however, this difference was statistically significant only at T3. There was also a significantly reduced overall growth increment in maxillary anterior alveolar height and anterior maxillary height in the PRS group.

The major difference between the two groups lay in the length of the mandible. The internal mandibular body length and mandibular length were significantly smaller in the PRS group across all three time points. PRS subjects appear to grow more vertically than ICP subjects, however the difference in gonial angle was only statistically significant at T1 and internal mandibular deflection at T1 and T2. Unlike the gonial angle, there was a significantly greater overall growth increment in internal mandibular deflection in the PRS group.

Table 16. Linear mixed model analysis of growth differences between PRS and ICP groups

<table>
<thead>
<tr>
<th>Measurements</th>
<th>T1 vs T2</th>
<th>T2 vs T3</th>
<th>T1 vs T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial Base</td>
<td>EMD</td>
<td>SE</td>
<td>P value</td>
</tr>
<tr>
<td>Cranial base angle (°)</td>
<td>0.246</td>
<td>0.529</td>
<td>0.642</td>
</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>0.19</td>
<td>0.398</td>
<td>0.633</td>
</tr>
<tr>
<td>Maxilla</td>
<td>EMD</td>
<td>SE</td>
<td>P value</td>
</tr>
<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>0.73</td>
<td>0.649</td>
<td>0.276</td>
</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>-0.109</td>
<td>0.468</td>
<td>0.816</td>
</tr>
<tr>
<td>Maxillary anterior apical width (mm)</td>
<td>0.311</td>
<td>0.361</td>
<td>0.39</td>
</tr>
<tr>
<td>Anterior maxillary height (mm)</td>
<td>0.088</td>
<td>0.259</td>
<td>0.733</td>
</tr>
<tr>
<td>Maxillary anterior alveolar height (mm)</td>
<td>0.613</td>
<td>0.352</td>
<td>0.082</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection (°)</td>
<td>3.476</td>
<td>3.402</td>
<td>0.308</td>
</tr>
<tr>
<td>Mandible</td>
<td>EMD</td>
<td>SE</td>
<td>P value</td>
</tr>
<tr>
<td>Condylion - Gonion - Anatomical Gnathion (°)</td>
<td>1.706</td>
<td>0.684</td>
<td>0.015</td>
</tr>
<tr>
<td>Mandibular length (Co-Gn)(mm)</td>
<td>0.889</td>
<td>0.848</td>
<td>0.295</td>
</tr>
<tr>
<td>Internal body length (mm)</td>
<td>0.562</td>
<td>0.646</td>
<td>0.385</td>
</tr>
<tr>
<td>Co-Gn (mm)</td>
<td>0.086</td>
<td>0.829</td>
<td>0.918</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>0.611</td>
<td>0.709</td>
<td>0.39</td>
</tr>
<tr>
<td>Ramal width (mm)</td>
<td>-0.88</td>
<td>0.537</td>
<td>0.103</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height (mm)</td>
<td>0.376</td>
<td>0.469</td>
<td>0.424</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>-0.456</td>
<td>0.42</td>
<td>0.279</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>0.414</td>
<td>0.443</td>
<td>0.351</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>-0.667</td>
<td>0.274</td>
<td>0.016</td>
</tr>
<tr>
<td>Symphyseal height (mm)</td>
<td>0.268</td>
<td>0.456</td>
<td>0.557</td>
</tr>
<tr>
<td>Symphyseal thickness (mm)</td>
<td>-0.224</td>
<td>0.223</td>
<td>0.315</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection (°)</td>
<td>-0.663</td>
<td>0.903</td>
<td>0.464</td>
</tr>
</tbody>
</table>

Growth differences PRS vs ICP - Mixed model

T1 vs T2 T2 vs T3 T1 vs T3
5.3. ICP vs Normal:

There were no significant differences in the cranial bases of the ICP and normal groups.

Maxillary lengths of the ICP groups were significantly deficient compared to the normal group at all three time points, with the most deficient growth increment occurring between T1 and T2.

ICP subjects had shorter mandibular lengths and internal body lengths which were statistically significant at T2 and T3 and significantly deficient overall growth from T1-T3. Symphyseal thickness, ramal length and width, anterior apical base width and posterior body height were deficient throughout growth. Subjects with ICP tended to grow more vertically than normal subjects with a significantly larger gonial angle at all three time points and significantly greater overall growth increments in gonial angle from T1 to T3. Internal mandibular deflection was significantly greater only at T3 with a statistically significant increase in the deflection between T2 and T3.

### Table 17. Linear mixed model analysis of growth differences between ICP and Normal groups

<table>
<thead>
<tr>
<th>Measurements</th>
<th>EMD</th>
<th>SE</th>
<th>P value</th>
<th>Sig</th>
<th>EMD</th>
<th>SE</th>
<th>P value</th>
<th>Sig</th>
<th>EMD</th>
<th>SE</th>
<th>P value</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial Base</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial base angle (o)</td>
<td>-0.529</td>
<td>0.529</td>
<td>0.319</td>
<td>No</td>
<td>0.505</td>
<td>0.529</td>
<td>0.341</td>
<td>No</td>
<td>-0.333</td>
<td>1.079</td>
<td>0.949</td>
<td>No</td>
</tr>
<tr>
<td>Anterior Cranial Base (SN) (mm)</td>
<td>0.716</td>
<td>0.419</td>
<td>0.088</td>
<td>No</td>
<td>0.349</td>
<td>0.419</td>
<td>0.406</td>
<td>No</td>
<td>-1.352</td>
<td>0.698</td>
<td>0.133</td>
<td>No</td>
</tr>
<tr>
<td>Maxilla</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxillary length (ANS-PNS) (mm)</td>
<td>2.193</td>
<td>0.707</td>
<td>0.002</td>
<td>Yes</td>
<td>0.981</td>
<td>0.707</td>
<td>0.166</td>
<td>No</td>
<td>-5.724</td>
<td>5.494</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Maxillary anterior basal width (mm)</td>
<td>0.309</td>
<td>0.47</td>
<td>0.511</td>
<td>No</td>
<td>-0.009</td>
<td>0.47</td>
<td>0.984</td>
<td>No</td>
<td>-1.064</td>
<td>0.322</td>
<td>0.004</td>
<td>Yes</td>
</tr>
<tr>
<td>Maxillary anterior apical width (mm)</td>
<td>-0.6</td>
<td>0.363</td>
<td>0.099</td>
<td>No</td>
<td>0.481</td>
<td>0.363</td>
<td>0.186</td>
<td>No</td>
<td>-0.542</td>
<td>0.22</td>
<td>0.04</td>
<td>Yes</td>
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<tr>
<td>Anterior maxillary height (mm)</td>
<td>0.623</td>
<td>0.261</td>
<td>0.018</td>
<td>Yes</td>
<td>-0.479</td>
<td>0.261</td>
<td>0.067</td>
<td>No</td>
<td>-0.726</td>
<td>0.212</td>
<td>0.002</td>
<td>Yes</td>
</tr>
<tr>
<td>Maxillary anterior alveolar height (mm)</td>
<td>0.007</td>
<td>0.356</td>
<td>0.848</td>
<td>No</td>
<td>0.121</td>
<td>0.356</td>
<td>0.734</td>
<td>No</td>
<td>0.332</td>
<td>0.321</td>
<td>0.558</td>
<td>No</td>
</tr>
<tr>
<td>Palatal/anterior maxillary deflection (o)</td>
<td>-4.488</td>
<td>3.412</td>
<td>0.19</td>
<td>No</td>
<td>3.047</td>
<td>3.412</td>
<td>0.373</td>
<td>No</td>
<td>1.395</td>
<td>1.76</td>
<td>0.708</td>
<td>No</td>
</tr>
<tr>
<td>Mandible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal mandibular deflection (o)</td>
<td>0.205</td>
<td>0.998</td>
<td>0.838</td>
<td>No</td>
<td>-2.249</td>
<td>0.998</td>
<td>0.025</td>
<td>Yes</td>
<td>3.118</td>
<td>1.043</td>
<td>0.009</td>
<td>Yes</td>
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<tr>
<td>Condylion - Gonion - Anatomical Gnathion (o)</td>
<td>-0.881</td>
<td>0.705</td>
<td>0.422</td>
<td>No</td>
<td>-0.486</td>
<td>0.705</td>
<td>0.491</td>
<td>No</td>
<td>6.122</td>
<td>1.119</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular length (Co-Gn)(mm)</td>
<td>0.581</td>
<td>0.958</td>
<td>0.544</td>
<td>No</td>
<td>0.112</td>
<td>0.958</td>
<td>0.907</td>
<td>No</td>
<td>-4.19</td>
<td>1.148</td>
<td>0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Internal body length (mm)</td>
<td>1.035</td>
<td>0.694</td>
<td>0.137</td>
<td>No</td>
<td>-0.005</td>
<td>0.694</td>
<td>0.989</td>
<td>No</td>
<td>-2.64</td>
<td>0.757</td>
<td>0.002</td>
<td>Yes</td>
</tr>
<tr>
<td>Co-Go (mm)</td>
<td>0.891</td>
<td>0.871</td>
<td>0.307</td>
<td>No</td>
<td>0.363</td>
<td>0.871</td>
<td>0.677</td>
<td>No</td>
<td>-3.664</td>
<td>0.875</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Internal ramal length (mm)</td>
<td>-0.374</td>
<td>0.749</td>
<td>0.617</td>
<td>No</td>
<td>0.942</td>
<td>0.749</td>
<td>0.21</td>
<td>No</td>
<td>-2.522</td>
<td>0.717</td>
<td>0.002</td>
<td>Yes</td>
</tr>
<tr>
<td>Ramal width (mm)</td>
<td>0.263</td>
<td>0.537</td>
<td>0.625</td>
<td>No</td>
<td>0.047</td>
<td>0.537</td>
<td>0.931</td>
<td>No</td>
<td>-2.195</td>
<td>0.547</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular posterior alveolar height (mm)</td>
<td>-0.588</td>
<td>0.471</td>
<td>0.214</td>
<td>No</td>
<td>0.499</td>
<td>0.472</td>
<td>0.295</td>
<td>No</td>
<td>-0.738</td>
<td>0.402</td>
<td>0.162</td>
<td>No</td>
</tr>
<tr>
<td>Mandibular posterior body height (mm)</td>
<td>1.088</td>
<td>0.421</td>
<td>0.01</td>
<td>Yes</td>
<td>-0.647</td>
<td>0.421</td>
<td>0.126</td>
<td>No</td>
<td>-2.331</td>
<td>0.296</td>
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<td>Yes</td>
</tr>
<tr>
<td>Mandibular anterior alveolar height (mm)</td>
<td>-0.651</td>
<td>0.442</td>
<td>0.142</td>
<td>No</td>
<td>-0.144</td>
<td>0.442</td>
<td>0.745</td>
<td>No</td>
<td>0.01</td>
<td>0.291</td>
<td>0.999</td>
<td>No</td>
</tr>
<tr>
<td>Mandibular anterior apical base width (mm)</td>
<td>0.284</td>
<td>0.274</td>
<td>0.301</td>
<td>No</td>
<td>0.263</td>
<td>0.274</td>
<td>0.338</td>
<td>No</td>
<td>-1.212</td>
<td>0.234</td>
<td>&lt;0.001</td>
<td>Yes</td>
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<tr>
<td>Symphyseal height (mm)</td>
<td>1.184</td>
<td>0.457</td>
<td>0.013</td>
<td>Yes</td>
<td>-0.4</td>
<td>0.457</td>
<td>0.382</td>
<td>No</td>
<td>-0.519</td>
<td>0.397</td>
<td>0.395</td>
<td>No</td>
</tr>
<tr>
<td>Symphyseal thickness (mm)</td>
<td>0.247</td>
<td>0.223</td>
<td>0.27</td>
<td>No</td>
<td>0.444</td>
<td>0.223</td>
<td>0.048</td>
<td>Yes</td>
<td>1.457</td>
<td>0.318</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandibular plane/symphyseal deflection (o)</td>
<td>0.456</td>
<td>0.904</td>
<td>0.613</td>
<td>No</td>
<td>1.428</td>
<td>0.904</td>
<td>0.115</td>
<td>No</td>
<td>-2.26</td>
<td>1.285</td>
<td>0.188</td>
<td>No</td>
</tr>
</tbody>
</table>
6. Discussion

The aim of this study was to investigate the craniofacial morphology and facial growth patterns in non-syndromic PRS and compare them longitudinally to race-, age- and sex-matched ICP and unaffected children during their active growth period. A true longitudinal analysis of such a long duration involving such a large sample size is lacking in the literature. Based on the results of our cephalometric analysis, significant differences in craniofacial growth patterns and morphology were found between the three groups, thus leading to the rejection of the null hypotheses.

The subjects diagnosed with PRS and ICP selected for this study were treated at the Hospital for Sick Children, where a large interdisciplinary team of experts including surgeons, orthodontists, pediatricians, syndromologists and clinical geneticists is involved in managing craniofacial abnormalities. Because of this, it was possible to confidently select patients with PRS and ICP who did not have any associated syndromes. In order to limit variability in the PRS and ICP groups and make sure that the craniofacial features seen were not due to any associated syndromes, it was important to separate syndromic from non-syndromic patients. Although none of the patients received orthognathic surgery or functional appliance treatment during the study period, they did receive fixed orthodontic appliance treatment at the center’s orthodontic clinic. For this reason, no dental measurements were included and evaluated in this study.

For the purposes of comparison and to serve as controls for different aspects of growth, an ICP group and an unaffected group were selected. The reason for selection of an ICP group was to control for aspects of craniofacial growth that may be affected by the presence of cleft palate and its surgical management. Maxillary dimensions in subjects with ICP have been noted to be smaller than normal before and after surgical repair (Shibasaki and Ross, 1969; Laitinen and Ranta, 1998). The deficiency in the maxilla may partly be due an innate developmental defect and partly due to fibrotic scar tissue formation as a result of surgical cleft repair (Ross and Coupe, 1965). Ross and Coupe (1965) as well as Shibasaki and Ross (1969) also identified that mandibles in patients with ICP displayed a positional change, most likely due to the altered maxillary complex. Palatal clefts result in Mandibles displaying a clockwise, downward and backward rotation resulting in increased gonial angles and increased lower face heights. These
mandibular changes are thought to be a characteristic of craniofacial growth in patients with isolated cleft palate since similar findings were seen in operated and un-operated subjects (Bishara, 1973; Dahl et al., 1982, 1989; daSilva et al., 1989; daSilva et al., 1992, 1993).

The unaffected group served as a second control group and was selected from the Burlington Growth Center archives. This group included subjects with class I occlusions and skeletal growth patterns as evaluated by mean ANB measurements of $3.24^\circ \pm 1.34^\circ$ by T3. In a survey conducted by Proffit et al. (1998), normal population consists of a range of occlusions, Class I – 80% - 85%, Class II – 15%, Class III – 1%. In spite of this range of malocclusions in the normal population, unaffected children with a Class I skeletal pattern and occlusion were selected for comparison to the PRS sample. This is because, during orthodontic treatment, the goal is ideally to achieve a class I occlusion and skeletalodontal relation. Therefore, in order to formulate a realistic treatment plan, it is important to know the discrepancies that exists between patients with PRS and the ultimate goal of such a class I occlusion and relation. Additionally, in order to reduce variability in the study sample that is attributable to race, the subjects in all three groups were limited to the Caucasian race.

Several studies investigating the craniofacial growth patterns of patients with PRS and ICP have consistently found that the greatest difference is between the PRS and the normal groups. The ICP group tends to be in between with more similarities to the PRS group than to the normal group (Figueroa and Friede, 2000). The superimposed averaged tracings of the three groups at each time point show that a similar trend was found in this study sample as well (Figure 3, 4 and 5). Through these images, it is apparent that the PRS group had the most retrusive mandibles that remained retrusive throughout the active facial growth period. However, their intermaxillary relationships appear to be harmonious. This is also evident from the mean ANB values (unadjusted) recorded in the PRS group over the three time points (T1: $5.83^\circ \pm 2.93^\circ$, T2: $4.39^\circ \pm 3.04^\circ$, T3: $4.00^\circ \pm 3.4^\circ$). The presence of a deficient maxilla significantly alleviates the appearance of the underdeveloped mandible, creating a bimaxillary retrognathic profile type. This facial profile pattern has also been reported by Matsuda et al, 2006; Suri et al, 2010a; Shen et al, 2012. As well, the PRS and ICP groups displayed the characteristic vertical growth pattern seen in subjects with palatal clefts, as described earlier.
Cranial base angle and anterior cranial base length was not an area of noteworthy difference between the three groups in this study. Although the anterior cranial base length measurement was shorter than normal in the PRS and ICP groups, this difference did not reach statistical significance at any of the three time points. Suri et al. (2010a) and Shen et al. (2012) found a significantly shorter anterior cranial base length in their PRS group when compared to normative values. Similar to the results of this study, Suri et al. (2010a) did not find a significant difference in angular cranial base measure between PRS and unaffected subjects. Comparable to the findings in the literature which generally reports no differences in the cranial bases of patients with PRS and ICP, this study found no differences in the cranial bases of subjects with PRS and ICP (Laitinen and Ranta, 1992; Laitinen et al., 1997; Daskalogiannakis et al., 2001; Shen et al., 2012).

Since patients with PRS and ICP undergo surgical palatal repair procedures, it is expected that their maxillary growth will be interrupted and their maxillary lengths, deficient. In this study, the maxillary lengths of PRS and ICP groups were not significantly different from each other, however, they were significantly shorter than the normal group. The averaged maxillary lengths of the PRS and ICP groups were approximately 10.8% (6.0mm) shorter than the normal group. The greatest maxillary growth differential occurred between T1 and T2, with an insignificant growth difference between T2 to T3. The maxillas of subjects with ICP and PRS grew at approximately half the rate of the maxillas of the unaffected group between T1 to T2 (2.7mm, 3.67mm and 6.55mm respectively). These findings are corroborated by several studies reported in the literature (Table 18) (Laitinen and Ranta, 1991, Bacher et al., 2000; Suri et al., 2010a; Shen et al., 2012). Several causes for deficient maxillary growth in cleft patients have been cited in the literature, most common of which are related to the surgical repair of the cleft and scar tissue formation. Other causes include, type and severity of the cleft, quality of pre- and postoperative care including orthodontic and prosthodontic intervention, lack of primary palatal tissue to support adequate midfacial growth, inability to perform normal functions which is a stimulus for normal maxillary growth and genetic abnormalities (Bishara, 1973; Satokata and Maas, 1994).
Generally, PRS and ICP were smaller in other areas of the maxilla as well, although, this difference was not always statistically significant. Alveolar portions of the maxilla were demarcated from the basal portions of the maxilla, showing reduced heights and widths in the alveolus of the PRS and ICP groups when compared to the unaffected group. The general reduction in maxillary volume could be attributed to bone and tissue deficiencies due to clefting and growth disruption due to post-surgical scar tissue formation. Another possible explanation for underdevelopment of the alveolus could be an abnormality in the MSX1 gene. The MSX1 gene, commonly implicated in cleft palate formation, is responsible for epithelial-mesenchymal interactions during embryogenesis. Aside from clefting of the palate, abnormality in the MSX1 gene also results in deficiency in the alveolar bone development of the maxilla and the mandible as well as tooth bud malformation and consequently hypodontia (Satokata and Maas, 1994). ICP and PRS populations have a higher rate of permanent tooth agenesis compared to the normal population. About 30% - 50% of patients with PRS and 30% of patients with ICP have congenitally missing teeth, the most common being the mandibular 2nd premolar followed by the maxillary lateral incisor (Margareta et al., 1998; Antonarakis and Suri, 2014). The absence of permanent tooth development could further contribute to reduced alveolar development in the anterior maxilla.

Laitinen and Ranta (1992) found that patients with PRS present a more severe but morphogenetically similar developmental anomaly of the mandible than patients with ICP. These findings are supported by the results of this study as well. When comparing the mandibles of the PRS and ICP groups with each other, the most remarkable difference that was seen consistently throughout growth was in the length of the mandible. Mandibular length (Co-Gn) in the PRS group was 4.7% shorter than the ICP group at T1, getting better with growth and ending at 4.2% shorter than the ICP group at T3. The averaged deficiency in mandibular length of the PRS group was 4.6% (5.0mm) compared to ICP group. Although Daskalogiannakis et al (2001) did not find that the mandibular length of their PRS group got better with time, the averaged percentage deficiency in mandibular length of their PRS group was also 4.6% (T1: 4.23%, T2: 5.3%, T3: 4.1%) compared to the ICP group (Table 18). When the mandible is separated into ramal and body components, the difference in mandibular length can be mostly attributed to deficiencies in the mandibular body. While the ramal width essentially remained the same in
both groups, the internal body length (RBS-Gn) of the PRS group was 9.4% shorter than the ICP group at T1, ending at 8.6% shorter than the ICP group at T3. Another area of difference between the PRS and ICP groups was in the degree of the vertical growth of the face. The gonial angle (Co-Go-Gn) and internal mandibular deflection angle (Co-RBS-Gn) of the PRS group were greater than the ICP group. This suggests an increased vertical pattern of growth in subjects with PRS compared to subjects with ICP, as supported by several studies in the literature (Daskalogiannakis et al., 2001; Shen et al., 2012).

As expected, mandibular morphology of the PRS and ICP groups significantly differed from the normal group at all three time points. The internal mandibular deflection angles, gonial angles and ramal height measures of the PRS group were significantly different from the normal group. Increased gonial angle and internal mandibular deflection angle along with reduced ramal length (7.4%) suggests a reduced posterior face height and a vertical pattern of growth. These results are in agreement with the associations made in the literature regarding palatal clefts and a vertical pattern of facial growth resulting in increased gonial angles and consequently, a posteriorly rotated mandible (da Silva et al., 1993; Suri et al., 2010a). Bishara (1973) and da Silva et al (1989 and 1992) found that these differences were not attributed to surgical repair of the cleft, but rather were a part of the craniofacial characteristics of cleft palate patients. True to form, the mandibular length of the PRS group was significantly shorter than the normal group and remained at approximately 92% (9.7mm) of normal mandibular length throughout the growth period. When the mandible is separated into ramal and body components, most of the deficiency appears to be in the body of the mandible. The internal body length of the PRS group remained approximately 13% shorter than the normal group, while the ramal width was 7.4% shorter than the normal group. Suri et al. (2010a) reported similar results with their PRS group displaying a 6.5% deficiency in mandibular length, 11.1% deficiency in internal body length and a 10.7% deficiency in ramal width compared to their normal group.

Compared to the normal group, the pattern of diminished mandibular growth did not change throughout T1 to T3. This is illustrated by the similar amount of mandibular growth experienced by both groups from T1 to T3 (23.1mm in the normal group vs 21.9mm in the PRS group). The findings from Figueroa et al (1991) suggest that the mandibles of babies with PRS experience a
greater change in mandibular length during the first 2 years of life than normal babies (53.5% change vs 38% change). However, this mandibular growth spurt is only enough to allow partial catch-up in mandibular length. Even though this growth spurt is limited, it is extremely important in improving the airway dimension and resolving the respiratory distress that infants with PRS experience immediately after birth.

Aside from a deficient mandibular length in the PRS group, it was also evident that their mandibles had significantly reduced bony volume. Symphyseal width (10.5%), mandibular posterior body height (16.3%) and mandibular anterior apical base width (9.2%) were all deficient compared to the normal group. Suri et al. (2010a) also found a significant reduction in mandibular bony volume when comparing the mandibles of the PRS group to the normal group. They found a symphyseal width deficiency of 9.6%, a posterior body height deficiency of 12.9% and mandibular anterior apical base width deficiency of 12%. In this study, the ICP group also displayed significant deficiencies in their mandibular bony volume (9.8% deficiency in symphyseal width, 22.8% deficiency in mandibular posterior body height and 13.4% deficiency in mandibular apical base width), suggesting that these deficiencies seen in both groups may be due to growth disturbances attributed to the palatal clefts.

Some of the strengths and limitations of this study should be considered when interpreting the results. Even though this study involves the largest racially homogenous sample of PRS to be reported in the literature till date (43 subjects), it is still a relatively small sample population. A major strength of this study was the use of a comprehensive cephalometric analysis that was not restricted to the use of external measurements. The analysis previously described by Suri et al. (2006, 2010b) involves internal measurements that are not affected by remodelling changes caused by muscle attachments on the surface. Using this analysis also allowed description of morphological features that have previously not been described, such as anterior maxillary basal and apical heights and widths, among several other measurements. Measurements such as internal ramal length, internal body length, posterior and anterior mandibular alveolar heights, posterior mandibular body height, symphyseal height, internal mandibular deflection and mandibular plane/symphyseal deflection were possible using the RBS point. Ramus Body syncline (RBS) is an internal geometrically constructed landmark that was used to differentiate
between the ramal components and body components of the mandible. It is the point of
intersection between the mid-planed cortical outline of the inferior alveolar nerve canal and a
line going through the posterior alveolar point on the mandible (PAPmd) and the inferior gonion
(Inf Go). Using inferior gonion avoids the use of gonion and antegonial notching which can both
affected by muscular attachments. A possible direction for similar future studies could involve
taking into account the morphological aspects of general somatic growth when considering the
inclusion criteria of their sample.

The results of this study do not support the decision for early treatment of patients with PRS
when it relates solely to their long term jaw relationship. Infants with PRS often require
treatment to resolve respiratory difficulties encountered at birth. On average, their maxillas and
mandibles both become retrognathic with growth, displaying a harmonious but bimaxillary
retrognathic profile type. Furthermore, the tendency for vertical growth and clockwise rotation of
the mandible implies that orthodontic mechanics increasing lower face height should be avoided.
Orthognathic surgery at the completion of growth may be useful for patients with PRS to
improve esthetics and facial balance, as well as to correct retrognathia in one or both jaws.
Table 18. Averaged percentage differences in maxillary and mandibular lengths found in this study in comparison with those reported in the literature.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Author</th>
<th>Study Design</th>
<th>Comparison Group</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary</td>
<td>Pereira et al. (2017)</td>
<td>Retrospective Longitudinal</td>
<td>PRS vs Normal</td>
<td>N - 43</td>
<td>6y-17y</td>
<td>10.8%</td>
</tr>
<tr>
<td></td>
<td>Suri et al. (2010a)</td>
<td>Retrospective Longitudinal</td>
<td>PRS vs Normal</td>
<td>N - 34</td>
<td>11y-17y</td>
<td>12.3%</td>
</tr>
<tr>
<td></td>
<td>Shen et al. (2012)</td>
<td>Longitudinal</td>
<td>PRS vs ICP</td>
<td>N - 43</td>
<td>6y-17y</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Shen et al. (2012)</td>
<td>Longitudinal</td>
<td>PRS: N -13 ICP: N -14</td>
<td>4y-13y</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pereira et al. (2017)</td>
<td>Retrospective Longitudinal</td>
<td>PRS vs ICP</td>
<td>N - 43</td>
<td>6y-17y</td>
<td>4.6%</td>
</tr>
<tr>
<td>Mandibular</td>
<td>Suri et al. (2010a)</td>
<td>Retrospective Longitudinal</td>
<td>PRS vs Normal</td>
<td>N - 34</td>
<td>11y-17y</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>Shen et al. (2012)</td>
<td>Longitudinal</td>
<td>PRS vs ICP</td>
<td>N - 43</td>
<td>6y-17y</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td>Shen et al. (2012)</td>
<td>Longitudinal</td>
<td>PRS: N -13 ICP: N -14</td>
<td>11y-17y</td>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daskalogiannakis et al. (2001)</td>
<td>Mixed Longitudinal</td>
<td>PRS: T1: 96; T2 &amp; T3: 38 ICP: 50</td>
<td>6y-17y</td>
<td>4.6%</td>
<td></td>
</tr>
</tbody>
</table>

* Some subjects included in the current study were also included in the studies by Daskalogiannakis et al. (2001) and Suri et al. (2010a)
7. Conclusions

In this true longitudinal study of the largest, racially homogenous PRS sample to be reported on to date, the following conclusions can be drawn:

- The craniofacial morphology and longitudinal facial growth in subjects with PRS and ICP differ significantly from comparable unaffected Class I children.

- The significant morphological differences lie in the mandible:
  - Mandibular length, ramal length, ramal width, symphyseal thickness and internal body length are significantly smaller in PRS and ICP groups in comparison to the unaffected group.

- Maxillary length is also remarkably deficient in both PRS and ICP subjects.

- The craniofacial morphology of PRS and ICP are similar in many areas except for an exaggerated deficiency in mandibular length and vertical growth pattern.

- Many of these morphological differences are seen at the 6yr time point and continue to be deficient throughout the active growth period, with little improvement over time.
8. References


