The Apert and Crouzon syndromes: General and dental aspects

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To my wife Chryssoula
and our daughters Paraskevi, Anna, and Artemis

Abstract

The Apert and Crouzon syndromes: General and dental aspects

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Background: Craniofacial malformations, as seen in Apert and Crouzon syndromes, may have an immense impact not only on function and esthetics, but also on the psychosocial well-being of the person affected.

Aims: To provide insight on the social life aspects of persons with Crouzon syndrome in Sweden, during the transition from childhood to adulthood and as young adults. Furthermore, to study the main facial and intraoral characteristics of persons with Apert or Crouzon syndrome, the clinical manifestations that may be present in addition to the main syndromic features, and the cranio-maxillofacial surgical treatment protocols followed. Finally, to investigate dental agenesis and dental agenesis patterns of permanent teeth in persons with these syndromes.

Material and Methods: Firstly, interviews according to the qualitative method of Grounded Theory were carried out. Eight persons with Crouzon syndrome participated. Then, 23 patients with Apert syndrome and 28 patients with Crouzon syndrome were evaluated for general aspects, craniofacial aspects, dentoalveolar traits before and after the final orthognathic surgery, types and timing of craniofacial surgical operations. Finally, dental agenesis and dental agenesis patterns were studied in 26 persons with Crouzon syndrome and in 23 individuals with Apert syndrome by evaluation of serial panoramic radiographs.

Results and Conclusions: The analysis of the interviews revealed that persons with Crouzon syndrome had to face different obstacles when developing their self-image during the transition from childhood to adulthood. Young adults with Crouzon syndrome tried to make the best of their situation. Already from childhood, they developed various strategies that helped them to cope with their lives. Mental disability, associated additional malformations, cleft palate, and extensive lateral palatal swellings were more common in children with Apert syndrome. In both syndromes, clinical findings included concave profile, negative overjet, posterior crossbites, anterior openbite, and dental midline deviation, which were significantly improved in almost all instances after the final combined orthodontic and orthognathic surgical treatment. The only exception was the posterior crossbites, which were persisting in about half of the cases. Cranial vault decompression and/or reshaping, midfacial and orbital advancement procedures, often in conjunction with a mandibular set-back, were the most frequent craniofacial operations performed in both of the syndromes investigated. The prevalence of agenesis for at least one tooth was 42.3% for the patients with Crouzon syndrome. The dental agenesis patterns showed a remarkable variability. The prevalence of agenesis for at least a tooth was 34.8% for the patients with Apert syndrome. Symmetrical and repetitive dental agenesis patterns were identified.

Key words: Apert syndrome, Crouzon syndrome, social life, grounded theory, clinical features, cranio-maxillofacial surgery, dental agenesis, dental agenesis patterns
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Preface

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-V):

I. Hallberg U, Stavropoulos D, Mohlin B, and Hagberg C. (2011): ***Living with Crouzon syndrome: Transition from childhood to adulthood.*** *Scand J Disabil Res* In press

II. Stavropoulos D, Hallberg U, Mohlin B, and Hagberg C. (2011): ***Living with Crouzon syndrome: How do young adults with Crouzon syndrome handle their life situation?*** *Int J Paed Dent* 21: 35-42

III. Stavropoulos D, Mohlin B, Kahnberg K-E, and Hagberg C. ***Comparing patients with Apert and Crouzon syndromes: Clinical features and cranio-maxillofacial surgical reconstruction.*** Submitted

IV. Stavropoulos D, Bartzela T, Mohlin B, Kahnberg K-E, and Hagberg C. ***Dental agenesis patterns in Crouzon syndrome.*** Submitted

V. Stavropoulos D, Bartzela T, Bronkhorst E, Mohlin B, and Hagberg C. (2011): ***Dental agenesis patterns of permanent teeth in Apert syndrome.*** *Eur J Oral Sci* In press

Abbreviations

A	sample size of persons with Apert syndrome
C	sample size of persons with Crouzon syndrome
Ca	permanent canine
CAN	Crouzon syndrome with acanthosis nigricans
CI	95% Confidence Interval
CVR	cranial vault decompression and/or reshaping
FDI	Fédération Dentaire Internationale (International Dental Federation)
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
FGFR2 gene	Fibroblast Growth Factor Receptor 2 gene
FGFR3 gene	Fibroblast Growth Factor Receptor 3 gene
GCC	Gothenburg Craniofacial Center
I_1	permanent central incisor
I_2	permanent lateral incisor
Ig	immunoglobulin-like domain of FGFR
IQ	Intelligence Quotient
M_1	permanent first molar
M_2	permanent second molar
mm	millimeters
NS	non-significant statistical difference
OB	openbite
OJ	overjet
P_1	permanent first premolar
P_2	permanent second premolar
Positive OB	positive overbite
Pro253Arg	substitution of the amino-acid arginine (Arg) for the amino-acid proline (Pro) at position 253
Q_1	upper right quadrant of the human dentition
Q_2	upper left quadrant of the human dentition
Q_3	mandibular left quadrant of the human dentition
Q_4	mandibular right quadrant of the human dentition
S	significant statistical difference
Ser252Trp	substitution of the amino-acid tryptophane (Trp) for the amino-acid serine (Ser) at position 252
T_1	shortly before the final combined orthodontic and orthognathic surgery treatment
T_2	shortly after the final combined orthodontic and orthognathic surgery treatment

TAC	Tooth Agenesis Code
$TAC_{overall}$	Tooth Agenesis Code for the entire mouth
TK	Tyrosine Kinase

Introduction

Nomenclature and historical perspective

Apert and Crouzon syndromes are rare developmental deformity syndromes, which are included in the clinical entity of *craniosynostoses*. This is a heterogeneous group of conditions, characterized by premature fusion of cranial sutures (Cohen, 2000a). A *suture* is a form of joint, in which the opposing bone margins in the craniofacial complex are joined with a thin layer of fibrous tissue (Persson, 1995). Sutures are important growth sites of the craniofacial skeleton (Enlow, 1966). Premature fusion of one or more sutures in the growing face results in growth retardation and underdevelopment of the midface and the cranium (Friede, 1995). Even as early as 1851, Virchov described the craniofacial deformity in cases with premature craniosynostosis as a result of *growth inhibition to the fused suture*, with *compensatory overexpansion of the cranium* at open sutural sites in order to accommodate brain growth (Kreiborg, 2000). This pathology gives rise to multiple anomalies of the craniofacial region, including the calvaria, the cartilaginous cranial base, the orbits and the maxillary complex (Kreiborg and Pruzansky, 1981; Kreiborg et al., 1993).

Apert syndrome or *acrocephalosyndactyly* was named after the French pediatrician Eugene Apert. In 1906, he described the condition that shows "tall skull, flat in the back and also at times on the side" and "*syndactyly* of the four limbs" (Apert, 1906). However, *craniosynostosis* combined with *syndactyly* (bony and cutaneous fusion of fingers and toes) had already been described earlier, in 1886, by Troquart (Perlyn et al., 2009).

Crouzon syndrome or *craniofacial dysostosis*, was named after the French neurologist Octave Crouzon. In 1912, he described the hereditary syndrome of *craniofacial dysostosis* in a mother and her son, presenting the characteristic triad of calvarial deformities, facial anomalies and exopthalmos (Crouzon, 1912). Nevertheless, the condition had already been reported earlier, in 1898, by Swanzy as "a case of microcephalus and proptosis" (Kreiborg, 1981). In the English literature it was not reported under the name of *craniofacial dysostosis* or *Crouzon syndrome* until 1939. Earlier investigations of this condition were presented under the term of *oxycephaly* (Kreiborg, 1981).

It appears that Apert thought that his cases represented the same condition as those reported by Crouzon, with the exception of the syndactyly of hands and feet; however, Crouzon argued that his cases and Apert's cases were separate conditions (Kreiborg and Cohen, 1998).

Clinical features

Apert syndrome is characterized by craniosynostosis, midfacial hypoplasia and symmetric syndactyly of the hands and feet, minimally involving the digits 2, 3, and 4 (Cohen, 1975). Crouzon syndrome shows craniosynostosis and midfacial hypoplasia (Kreiborg, 1981). Crouzon syndrome with acanthosis nigricans (CAN) accounts for around 5% of patients with this syndrome. It is a clinical type of Crouzon syndrome with the additional manifestation of pigmented hyperkeratotic patches (brown to black velvet stains) in dermal folds, such as the neck or under the arm (Reddy et al., 1985). CAN has been postulated to be an independent clinical entity (Cohen, 1999), with more severe manifestations, such as brain malformation and choanal atresia, which are unusual in classic Crouzon syndrome (Arnaud-Lopez et al., 2007). Apert and Crouzon syndromes show variable clinical severity, ranging from mild to severe (Kreiborg, 1981; Cohen and Kreiborg, 1996).

Both conditions share a number of common craniofacial features (Kreiborg, 1981; Cohen, 2000b), most importantly the premature fusion of the cranial sutures. The fusions result in secondary growth and/or developmental disturbances. These include brachycephally, short cranial fossa, enlarged cella turcica, wide cribriform plate, shallow orbits, ocular proptosis, hypertelorism, short nose with deviated nasal septum, narrow nasal cavity, and diminished nasopharyngeal space. Further features are maxillary hypoplasia, narrow and arched palate and dental malocclusion, such as negative overjet, anterior openbite, posterior crossbite, and severe dental crowding. Dental agenesis of permanent teeth has been reported both for Apert (Dalben Gda et al., 2006b; Letra et al., 2007) and for Crouzon syndrome (Kreiborg, 1981; Burzynski and Escobar, 1983; Jeftha et al., 2004). Figures 1 and 2 depict the main characteristics of the two syndromes in drawings with varying severity of craniofacial disfigurement.

However, these two syndromes show marked differences (Kreiborg and Pruzansky, 1981; Kreiborg and Cohen, 1992; Kreiborg et al., 1993; Cohen and Kreiborg, 1996; Kreiborg and Cohen, 1998). Patients with Apert syndrome show premature fusion of mainly the coronal cranial sutures at birth. In addition, they have a wide midline calvarial defect extending from the glabella to the posterior fontanelle. During the first two to four years of life, it becomes obliterated by coalescence of bony islands, formed in the defect (Kreiborg and Cohen, 1990). The Crouzon infant calvaria show more extensive synostosis of the cranial sutures, with no defect in the midline. Thus, newborns with Crouzon syndrome have a high risk of developing an increased intracranial pressure (Renier et al., 2000), due to the fused cranial bones forming a "rigid box" around the growing brain, leading to severe neurological consequences. Moreover, in Apert syndrome the cranial vault takes an accrocephalic (tower-like) shape, which is not encountered in Crouzon syndrome. Furthermore, asymmetric cranial base and platybasia (excessively

obtuse cranial base angle) are more common in Apert syndrome. Facial asymmetry is also frequent in these persons. The Apert mouth is trapezoidal-shaped at rest. Cleft palate or bifid uvula is common (70%). In Crouzon syndrome, cleft lip and cleft palate are rare (2% and 3%, respectively), and a bifid uvula occurs in 10%. Lateral palatal soft tissue swellings, which contain mucopolysacharides, are more common and more pronounced in Apert syndrome.

Apart from the syndactyly of the hands and feet, many associated pathologic manifestations can be noted in Apert syndrome. Brain malformations are not rare (Cohen and Kreiborg, 1990). Intelligence in Apert patients varies and more than half of these patients are considered to have an intellectual ability in the borderline range or less (Patton et al., 1988; Sarimski, 1997). Skeletal abnormalities, apart from the cervical spine fusions, which occur in 70% (Kreiborg et al., 1992), may also be present (Cohen and Kreiborg, 1993a). Cardiovascular and genitourinary anomalies occur for each of both conditions in around 10% (Cohen and Kreiborg, 1993c). In Apert syndrome, dermatologic manifestations, such as skin dimples, oily skin, excess sweating, and acneiform lesions are very common (Cohen and Kreiborg, 1995).

Associated malformations in Crouzon syndrome include several abnormalities of the central nervous system (Kreiborg, 1981; Cinalli et al., 1995). Nevertheless, intelligence is usually normal in the vast majority of these persons (Kreiborg, 1981). Fusions of the cervical vertebrae are reported in around 18% (Anderson et al., 1997). Furthermore, calcification of the stylohyoid ligament has been found in almost 90%, and atresia of the external auditory canals in around 10%. (Kreiborg, 1981) Solid cartilaginous trachea has also been observed (Devine et al., 1984). Orthopedic symptoms include stiffness of joints, especially the elbows (Kreiborg, 1981).

Etiology

Both syndromes are congenital disorders, inherited in autosomal dominant mode of transmission (Carinci et al., 2005). Different point mutations in the gene encoding the type 2 fibroblast growth factor receptor (*FGFR2*) have been found causal for Apert (Wilkie et al., 1995) and Crouzon syndrome (Reardon et al., 1994). This gene has been mapped to the long arm of the human chromosome 10 (Mattei et al., 1991). CAN has been associated with mutations in the *FGFR3* gene (Meyers et al., 1995).

The fibroblast growth factor receptors (FGFRs), which belong to the family of tyrosine kinase (TK) receptors, span the cellular membrane (transmembrane receptors). They transduce extracellular signals to the cytoplasm, by the binding of their ligands, the fibroblast growth factors (FGFs). The protein structure of FGFRs

is composed of an extracellular ligand-binding region, with three (I, II, and III) immunoglobulin-like (Ig) domains, a transmembrane domain, and two intracellular TK subdomains (Bonaventure and El Ghouzzi, 2003). Almost 99% of the reported cases with Apert syndrome carry one of two specific point mutations (Ser252Trp and Pro253Arg) in the linker region connecting the Ig-II and Ig-III domain of FGFR2 (Oldridge et al., 1999). About 30 different mutations, with almost all of them located on the Ig-III domain of the FGFR2, have been identified in patients with Crouzon syndrome (Reardon et al., 1994; Passos-Bueno et al., 1999).

These mutations result in inappropriate activation of the FGFRs by defective function, including ligand-independent signaling, altered ligand-binding specificity, and prolonged duration of receptor signaling (Bonaventure and El Ghouzzi, 2003). Several cellular mechanisms may contribute to premature sutural fusion in craniosynostosis, such as increased osteoblast differentiation and maturation (Ornitz and Marie, 2002).

Epidemiology

Birth prevalence in Apert and Crouzon syndromes is similar and estimated from 10 to 16.5 per million live births (Table 1).

Table 1

Birth prevalence (per million live births) in Apert and Crouzon syndromes

Apert syndrome		***Crouzon syndrome***	
Birth prevalence	Author and year	Birth prevalence	Author and year
10	(Czeizel et al., 1993)	11	(Czeizel et al., 1993)
12.5	(Tolarova et al., 1997)	15.5	(Martinez-Frias et al., 1991)
12.7	(Martinez-Frias et al., 1991)	16.5	(Cohen and Kreiborg, 1992a)
13.7	(Cohen and Kreiborg, 1992b)		
15.5	(Cohen et al., 1992)		

Birth prevalence varies for Apert syndrome among different ethnic groups. Asians show the highest birth prevalence per million live births (22.3), followed by Whites (16.6) and Hispanics (7.6) (Tolarova et al., 1997). Rare case reports for the Black population have also been acknowledged (Cohen, 2000b). No gender predilection has been reported for Apert syndrome (Cohen and Kreiborg, 1991). This condition accounts for 4.5% of all cases of craniosynostosis (Cohen et al.,

1992). Almost all of new cases are sporadic and represent mutations exclusively of paternal origin (Moloney et al., 1996). The rarity of familial cases has been attributed to the reduced likelihood of mating, due to the severe malformations associated with the condition (Cohen and Kreiborg, 1991). Sporadic births with Apert syndrome increase exponentially with paternal age. This has been attributed to an increase of frequency with causative mutations (Glaser et al., 2003), along with a selective advantage for these in the male germ line (Goriely et al., 2003).

In a comprehensive study of 61 persons with Crouzon syndrome (Kreiborg, 1981), 95% were Caucasian and 5% belonged to the Black population. Fifty four percent of the persons investigated were males. Crouzon syndrome accounts for around 5% of all cases of craniosynostosis (Cohen and Kreiborg, 1992a). Around half of new cases are familial (al-Qattan and Phillips, 1997). Advanced paternal age has been noted for fathers of persons with the syndrome (Glaser et al., 2000). The authors of the last study suggested that older men either have accumulated or are more susceptible to a number of germ line mutations.

Diagnosis

Apert syndrome has been diagnosed early in pregnancies with a positive family history for the syndrome by several modalities. Fetoscopy (Leonard et al., 1982), most often used in the past, is seldom used nowadays. Ultrasonography in families at risk has detected syndactyly in fetus of 16-17 weeks (Narayan and Scott, 1991). In a not-at-risk family, fetal ultrasound findings of syndactyly of the hands, clover-leaf skull, and ocular proptosis resulted in prenatal diagnosis in the 19th week of gestation (Skidmore et al., 2003). Nevertheless, the craniofacial characteristics of Apert syndrome may be very subtle during the second trimester of fetal life. As such, new cases from unaffected families usually become initially obvious in the third trimester, following routine ultrasonography (Pooh et al., 1999), or are identified at birth by their marked syndromic clinical features. Furthermore, genetic analysis (Filkins et al., 1997; Chang et al., 1998) is a valuable diagnostic tool. Magnetic resonance imaging also contributes to the diagnosis (Boog et al., 1999; Quintero-Rivera et al., 2006).

Ultrasonographic diagnosis of Crouzon syndrome in pregnancy with a positive family history for the syndrome has been set in 21 weeks of gestation, on the basis of detected hypertelorism (Leo et al., 1991). Exophthalmos has been documented in a 35-week Crouzon fetus (Menashe et al., 1989). First trimester molecular diagnosis of Crouzon syndrome has also been reported (Schwartz et al., 1996). Nevertheless, potential phenotypic overlapping of syndromes for the same mutation should be taken into consideration. For instance, identical *FGFR2* mutations have been found to cause both Crouzon and Pfeiffer syndromes (Rutland

et al., 1995). Some affected persons with very mild clinical features of Crouzon syndrome are detected only due to being related to a classically affected family member (Kreiborg, 1981).

Patients with craniosynostosis are usually studied with plain radiography and three dimensional computed tomography (Vannier et al., 1989; Kreiborg et al., 1993). Cephalometric radiography has been used to assess the craniofacial morphology of Apert and Crouzon syndromes (Kreiborg, 1981; Kreiborg et al., 1999), and also to compare them (Kreiborg and Cohen, 1998). The craniofacial phenotypes of these syndromes show the most pronounced differences during infancy, but become less exaggerated with age (Cohen, 2000b).

Syndrome-related problems

Hydrocephalus (excessive accumulation of cerebrospinal fluid in the brain) is a complication that may result in neurologic impairment or death, if not treated early. It is more frequently observed with Crouzon syndrome than with Apert syndrome (Collmann et al., 1988).

The midfacial retrusion observed in these syndromes can result in nasopharyngeal and oropharyngeal space of lower volume. This, in combination with potential posterior nasal choanae stenosis, may cause chronic mouth breathing, respiratory problems, obstructive sleep apnea, cor pulmonale, or even sudden death (Peterson-Falzone et al., 1981).

Most eye pathology in the two syndromes is caused by shallow orbits with ocular proptosis. The most common cause of visual impairment is amblyopia (poorly transmitted visual stimulation to the brain), followed by optic nerve atrophy. Ophthalmologic sequelae in Apert and Crouzon syndromes may include refractive errors (34% and 77%, respectively), divergent strabismus (60% and 39%, respectively), amblyopia (14% and 21%, respectively), exposure keratopathy (8% and 15%, respectively), and optic nerve atrophy (8% and 7%, respectively) (Gray et al., 2005; Khong et al., 2006).

Hearing loss has been reported to be as high as 90% in Apert syndrome (Zhou et al., 2009), and more than 50% in Crouzon syndrome (Orvidas et al., 1999). Inner ear anomalies and frequent otitis media associated with obstruction of the epipharyngeal space and cleft palate, are reported as some of the main causes for this clinical condition (Cohen and Kreiborg, 1993b; Zhou et al., 2009).

Children with Apert or Crouzon syndrome are expected to have considerable speech and language difficulties. This may depend on the fact that many of those with Apert syndrome demonstrate varying degree of mental disability; marked hearing loss and serious deformities in oral structures are other factors that have

been assessed to adversely affect speech (Elfenbein et al., 1981; Sininger et al., 1999). Social stimulation influences speech development (Goldstein et al., 2003). Impaired social interaction, due to the psychosocial impact of the craniofacial disfigurement, may further have a negative effect on the development of speech and language. In a study in children with Apert syndrome, expressive language skills and output have been reported to be considerably reduced outside the home, particularly at school and in group situations (Shipster et al., 2002).

Oral hygiene status in Apert and Crouzon syndrome has been sparsely focused on to date. The available research on this aspect suffers from inhomogeneous study groups and small sample sizes. Therefore, the conclusions from the available studies should be considered with caution. Children with Apert or Crouzon syndrome have been found to have higher plaque and gingival inflammation than healthy children (Mustafa et al., 2001). The oral structural deformities, along with scars due to surgical interventions, as well as the use of orthodontic appliances, may pose difficulties to plaque control (Wong and King, 1998). However, the higher risk of dental plaque in patients with Apert or Crouzon syndromes has not been associated with a higher risk for caries (Mustafa et al., 2001; Dalben Gda et al., 2006a).

Social and psychological impact

The human face plays a unique and critical role in social interactions and the development of the personality (Cole, 1998). As such, visible difference, as observed in people with Apert and Crouzon syndromes, may be thought of as a social disability. Children with craniofacial anomalies show dissatisfaction with facial appearance, which is related to greater loneliness, fewer same-sex close friends, social withdrawal, and dislike by peers (Pope and Ward, 1997). Potential problems in these children have been described to be the low cognitive development, negative emotional attachment between the child and parents, impaired development of peer relations, and experience of shame (Pruzinsky, 1992).

Teenagers with facial differences may have negative experiences during adolescence (Charkins, 1996). This is a unique period, framed by social and media norms. Those with a facial deviation may stronger feel the pressures caused by the series of images of "beautiful" people presented in different media sources (Rumsey and Harcourt, 2004).

The facially disfigured often experience traumatically offensive remarks, unpleasant stares, stunned reactions, and outright avoidance (Macgregor, 1990). Responses from others may strongly affect the self-concept. This is due to the self-esteem system, which assesses the extent to which someone is accepted or rejected

by others (Leary and Downs, 1995). Furthermore, people born with craniofacial disfigurement experience discrimination in employment or social settings (Sarwer et al., 1999).

Cranio-maxillofacial surgical reconstruction

Patients with Apert or Crouzon syndromes require a multi-disciplinary treatment approach, involving the coordinated team work of many medical, dental, and behavioral specialists. These professionals are needed to treat both the physical and psychosocial needs of the patients (David, 2003).

The cranio-maxillofacial surgical reconstruction of patients with these syndromes follows a series of staged procedures, tailored to the individual's needs (Posnick and Ruiz, 2000; Panchal and Uttchin, 2003):

- Stage I: Primary cranio-orbital decompression by advancement of the fronto-orbital bar (Hoffman and Mohr, 1976), including suture release, between the ages of 3 to 11 months. Repetitive craniotomy, for additional cranial vault decompression and reshaping, may be necessary.
- Stage II: Correction of the deformity of the midface, with monobloc fronto-orbital and midfacial advancement (Ortiz-Monasterio et al., 1978), Le Fort III osteotomies (Gillies and Harrison, 1950), or distraction osteogenesis techniques in severe cases, by the age of 4 to 7 years. The latter surgical techniques are gradual bone lengthening techniques by the employment of distraction devices that separate the bony segments at the osteotomies sites (Ilizarov, 1971; Polley and Figueroa, 1997).
- Stage III: Correction of cranial vault dysplasia between the ages 4 to 7 years.
- Stage IV: After full skeletal maturity, performance of Le Fort III midface surgical advancement and/or Le Fort I maxillary surgical advancement (Bell, 1975; Epker and Wolford, 1975), often in conjunction with a mandibular set-back osteotomy (Trauner and Obwegeser, 1957) to improve appearance and dental occlusion.

Additional surgical interventions may be needed, such as shunt surgery (neurosurgical operation to reduce intracranial pressure), tracheostomy in instances of severe airway obstruction, cleft palate plastic surgery, rhinoplasty, oculoplasty, or surgical eyelid closure. Patients with Apert syndrome have been reported to have the highest incidence of revision surgery in order to improve the forehead contour (Wong et al., 2000).

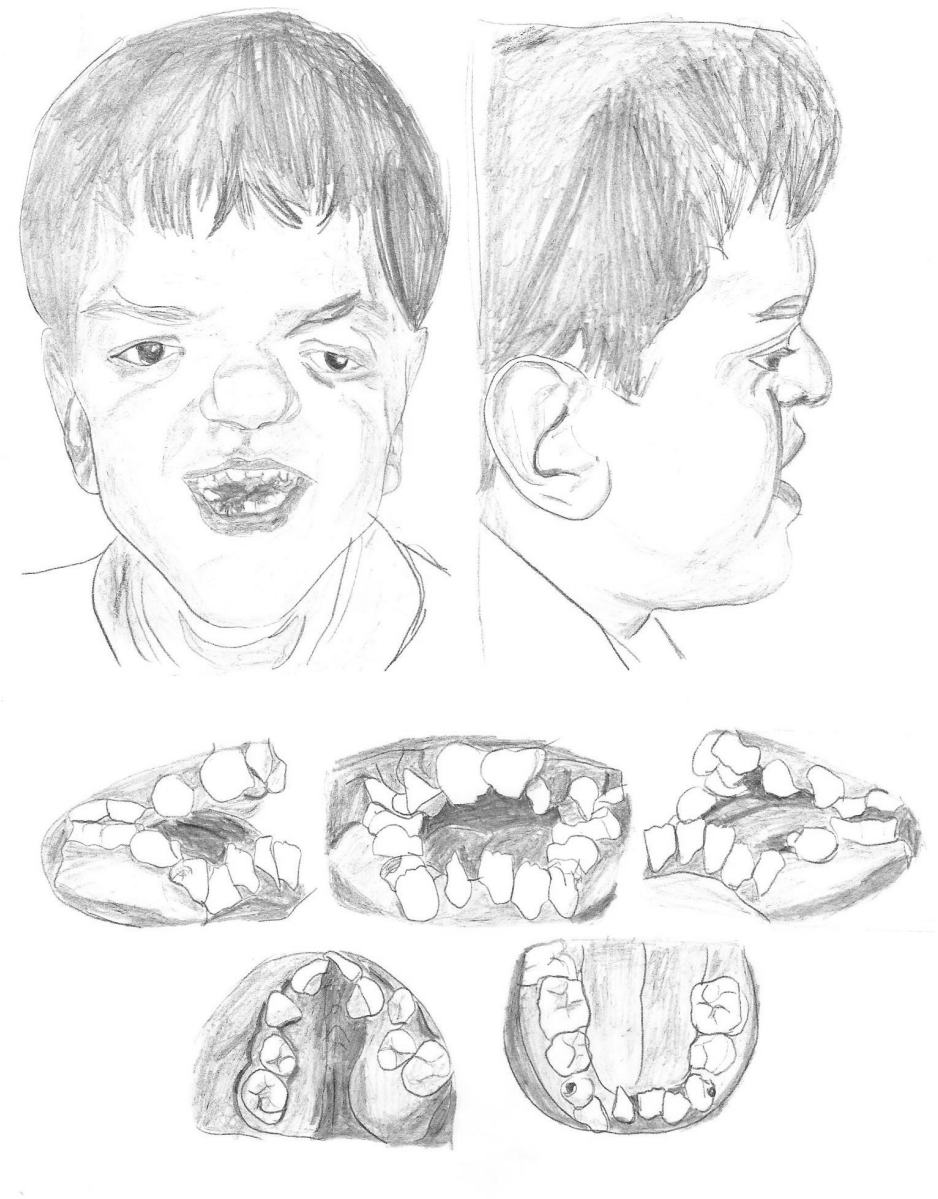

Figure 1: Drawings depicting the main clinical features of Apert syndrome.

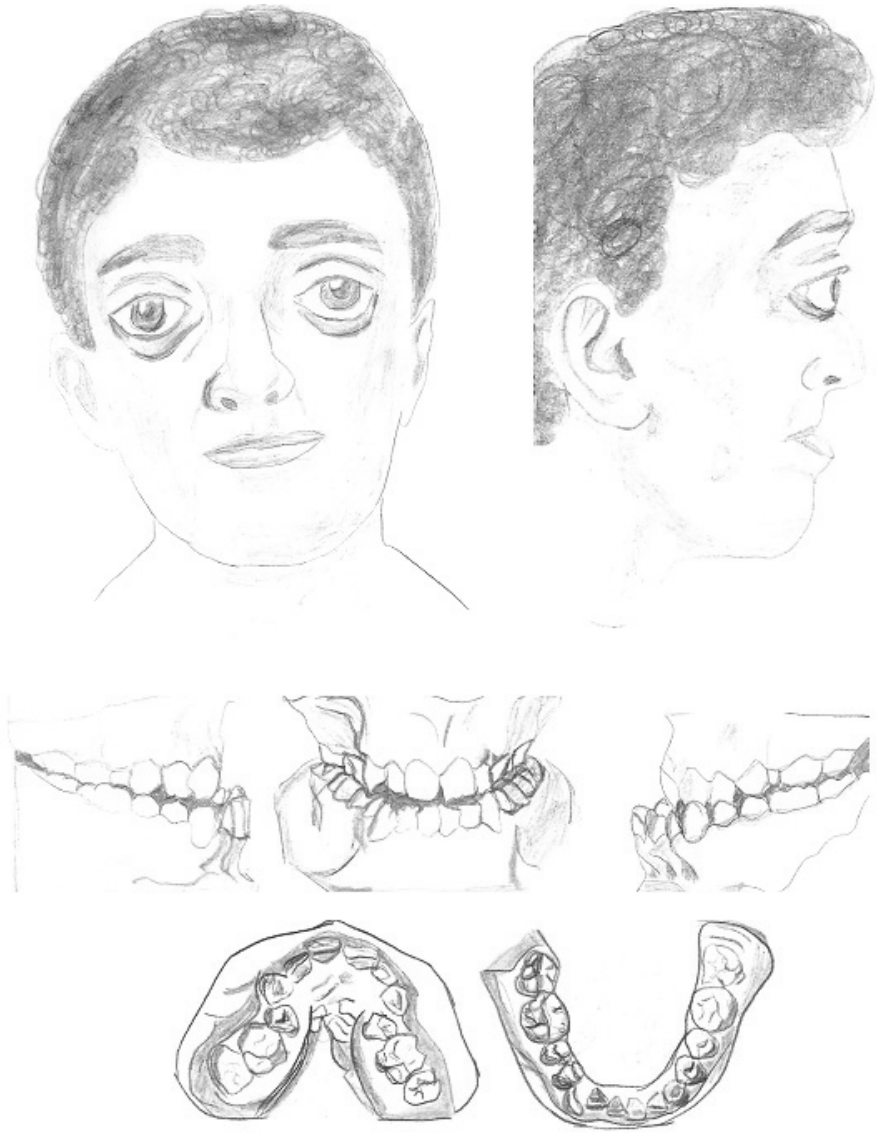

Figure 2: Drawings depicting the main clinical features of Crouzon syndrome.

Aims

The general aim of this research work was to deepen the understanding on general medical, dental, and psychosocial aspects of patients with Apert or Crouzon syndrome. Subjective and objective characteristics of these conditions were sought. In particular, specific aims for the five studies of the thesis were:

- To provide insight on the social life aspects of persons with Crouzon syndrome in Sweden, during the transition from childhood to adulthood (Study I).
- To explore how young adults with Crouzon syndrome handle their life (Study II).
- To study the main facial and intraoral characteristics of persons with Apert or Crouzon syndrome, the clinical manifestations that may be present in addition to the main syndromic features, and the cranio-maxillofacial surgical treatment protocols followed (Study III).
- To investigate dental agenesis and dental agenesis patterns in persons with Crouzon syndrome (Study IV).
- To investigate dental agenesis and dental agenesis patterns in persons with Apert syndrome (Study V).

Material and Methods

Subjects

The study population, in all five studies, was comprised of persons with Caucasian ethnicity and medically confirmed diagnosis of Apert or Crouzon syndrome. All of them had been treated consecutively at the Craniofacial Center at the Sahlgrenska University Hospital and were registered and therapy planned at the Section of Jaw Orthopedics of the Gothenburg University Clinic in Sweden (Gothenburg Craniofacial Center, GCC). They were born between the years 1970-1998. During this period of time, all Swedish children born with these syndromes were transferred to the GCC.

Study I: Living with Crouzon syndrome: Transition from childhood to adulthood.
Study II: Living with Crouzon syndrome: How do young adults with Crouzon syndrome handle their life situation?

A letter informing about the study was sent to adults 18 years old or older with either Apert syndrome or Crouzon syndrome. A reminder was sent after a month. Only persons with Crouzon syndrome responded positively to the first invitation (Figure 3). The mean age was 25.4 years. They had a variable range of clinical features typical for the syndrome and had undergone several sessions of cranio-maxillofacial surgery, starting from early childhood.

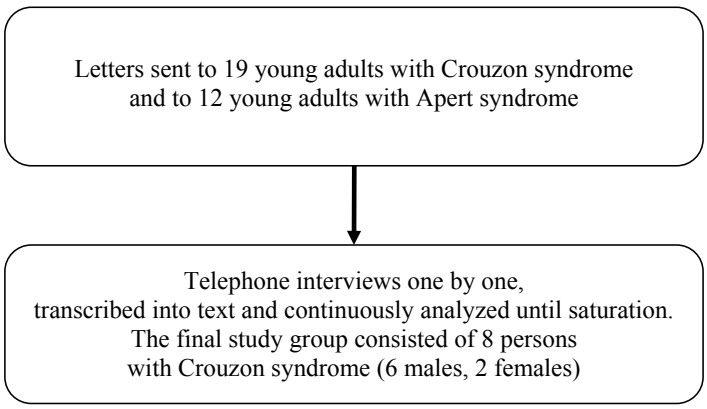

Figure 3. Subject recruitment in Studies I and II.

Study III: Comparing patients with Apert and Crouzon syndromes: Clinical features and cranio-maxillofacial surgical reconstruction.

The study groups were total samples of children registered with the medically confirmed diagnoses of Apert or Crouzon syndrome. They were born between the years 1970-1998. The inclusion criteria were:

- To be of Caucasian origin.
- To have been referred to GCC during the first year of life.

There were 23 persons with Apert syndrome (6 males, 17 females) and 28 persons with Crouzon syndrome (20 males, 8 females) who fulfilled the criteria. The study groups are presented in Figure 4.

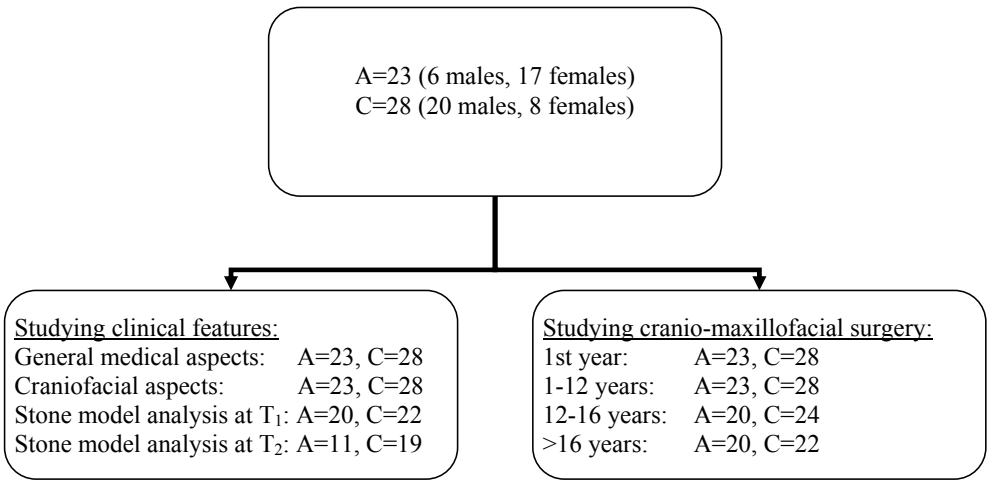

Figure 4. Subject recruitment in Study III. A: Sample size of persons with Apert syndrome; C: Sample size of persons with Crouzon syndrome; T_1: Shortly before final combined orthodontic and orthognathic surgery treatment (median age of persons with Apert syndrome: 15 years, range: 11-17 years; median age of persons with Crouzon syndrome: 15 years, range: 13-19 years); T_2: Shortly after finished orthodontics and orthognathic surgery treatment.

Study IV: Dental agenesis patterns in Crouzon syndrome.
Study V: Dental agenesis patterns of permanent teeth in Apert syndrome.

Panoramic radiographs were evaluated from all children with medically confirmed diagnosis of Apert or Crouzon syndrome, born between the years 1970-1998. All of them were treated consecutively at GCC. The inclusion criteria were:

- To be of Caucasian ethnicity.
- To be at least 8 years old at the time of the last panoramic radiographic examination. A panoramic radiograph from at least 11 years of age had to be available before a diagnosis of agenesis of second premolars was set.
- Identified cases with dental agenesis should be possible to be cross-checked with the person's dental records, in order to exclude premature extractions.

The study groups that fulfilled the inclusion criteria are presented in Figure 5. All, except for two subjects, were at least 11 years old at the time of the last panoramic radiographic examination. Those two 8 years old (one person with Apert syndrome and one person with Crouzon syndrome) were included, since they did not miss any permanent teeth according to their panoramic radiograph from 8 years of age.

Study IV: C=26 (20 males, 6 females)
Study V: A=23 (5 males, 18 females)

Figure 5. Subject recruitment in Studies IV and V. A: Sample size of persons with Apert syndrome; C: Sample size of persons with Crouzon syndrome.

Methods

Study I: Living with Crouzon syndrome: Transition from childhood to adulthood. Study II: Living with Crouzon syndrome: How do young adults with Crouzon syndrome handle their life situation?

Telephone interviews lasting up to 90 minutes were scheduled with each participant. The interviews were held in a conversational style and were open ended and tape recorded. All participants were asked about their lives starting from their childhood until the present age. An interview guide was used which covered themes such as childhood, school situation, relations with friends and family (Study I), as well as daily life, thoughts about meeting a partner, friends, and thoughts about the future (Study II). The participants had the opportunity to ask subjectively important questions regarding the area under study. In this process, the interviewer asked relevant follow-up questions. Data was generated within the active involvement of both the interviewer and the informant. Each interview was analyzed and served as a guide to the next one.

The audio-taped interviews were transcribed into text (verbatim transcribed interviews) for analysis. Data analysis was performed following a qualitative

research method, the Grounded Theory (Glaser and Strauss, 1967; Strauss and Corbin, 1998; Charmaz, 2000). Qualitative research involves the systematic collection, organization, and interpretation of textual material derived from talk or observation (Malterud, 2001). Grounded Theory is an inductive research method, usually employed in the exploration of relatively poorly investigated social phenomena. Its methods consist of systematic, yet flexible guidelines for collecting and analyzing qualitative data to construct theories/hypotheses "grounded" in the data itself in order to explain the phenomenon under study (Charmaz, 2006). Grounded Theory emphasizes on social dynamics. It has its theoretical roots in the sociological theory of *symbolic interactionism*, which assumes that people construct meanings about their lives on the basis of interactions they have with other people and the world at large (Blumer, 1969).

Following the method of Grounded Theory, the verbatim transcribed interviews were read line-by-line and were analyzed by a specific coding system (Strauss and Corbin, 1998). This system included *open coding*, assignment of codes to segments of text that depict what each segment is about; *axial coding*, comparing open codes with each other in order to define ideas that best fit and interpret the data as tentative analytic categories; *selective coding*, using frequently occurring codes to make a core category, central in the data and related to all other categories. According to Grounded Theory, when new interviews bring no additional information, it is said that *saturation* is reached (Charmaz, 2000).

Study III: Comparing patients with Apert and Crouzon syndromes: Clinical features and craniofacial surgical reconstruction.

Data was collected from patient charts and dental stone models. The evaluated stone models were the ones taken shortly before the final orthognathic surgery and when post-orthognathic surgery orthodontic treatment was completed. One damaged stone model was excluded from the analysis of the dental midlines, in one case with Apert syndrome. Overjet, overbite and midline deviation were registered in the dental stone models in millimeters to the closest integral digit. The following intervals were set for each registration:

- Overjet negative intervals: >10, 10 to >6, 6 to 1
- Overjet positive intervals: 0 to 6, >6
- Overbite negative intervals: >8, 8 to >4, 4 to 1
- Overbite positive intervals: 0 to 4, >4
- Midline deviation intervals: 0 to 3, >3 to 6, >6

All assessments were performed twice, by two investigators (DS, CH). In dubious cases, a discussion was made before a consensus was reached. Data for males and females was pooled.

Study IV: Dental agenesis patterns in Crouzon syndrome.
Study V: Dental agenesis patterns of permanent teeth in Apert syndrome.

Panoramic radiographs were evaluated for congenitally missing teeth, without including the third molars in the assessments. They were cross-checked with each case's dental record to exclude premature extractions. Absent teeth were registered according to the Fédération Dentaire Internationale (FDI) system (Peck and Peck, 1996). One observer (DS) scored all radiographs twice. Both assessments rendered exactly the same data, with the exception of a single case with Crouzon syndrome where the agenesis of a maxillary second molar was missed in the second evaluation. The opinion of a second observer (CH) was sought to reach a consensus for this case.

A numeric coding system, the Tooth Agenesis Code (TAC) (van Wijk and Tan, 2006), was used to describe patterns of dental agenesis of permanent teeth. According to this system, a specific value is assigned to each absent tooth (Table 2).

Table 2
Schematic representation of the human permanent dentition and application of binary arithmetic to assign unique values to the pattern of dental agenesis

	Q_1								Q_2							
A:	18*	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28*
B:	128	64	32	16	8	4	2	1	1	2	4	8	16	32	64	128
A:	48*	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38*
	Q_4								Q_3							

**Not included in the present study.*
Line A: Tooth numbering according to FDI system.
Line B: Values assigned to absent teeth. The tooth value, corresponding to an absent tooth, is determined by calculating $2^{(n-1)}$, in which n = the tooth number (1-8).
Q_1, Q_2, Q_3, Q_4: First to fourth quadrant of the dentition.

The values obtained for missing teeth are summed up for each quadrant of the dentition, generating a unique value that represents the dental agenesis pattern of each quadrant, the TAC. For example, if one central incisor (value: 1) and one

first molar (value: 32) are missing in a quadrant of a dentition, then the corresponding TAC value is: TAC=1+32, or TAC=33. If all teeth are present in a quadrant of the dentition of interest, then TAC=0. If all teeth are absent in a quadrant of the dentition of interest, then TAC=255.

Extending the application of this coding system to the entire dentition of an individual, a new variable is produced, the $TAC_{overall}$ (Creton et al., 2007). It is composed of the TAC of each quadrant, generating a unique number, which when written using decimal points to separate the TAC of each quadrant, permits the underlying TAC scores to remain recognizable. For example, when a $TAC_{overall}$ is 007.048.032.080, the number 007 corresponds to the TAC of the first quadrant of the dentition, the 048 to the TAC of the second, the 032 to the TAC of the third, and the 001 to the TAC of the fourth. Thus, the $TAC_{overall}$ variable may be described as follows:

$TAC_{overall}=TAC_{Q1}.TAC_{Q2}.TAC_{Q3}.TAC_{Q4}$, in which TAC_{Q1}=TAC for Q_1, TAC_{Q2}=TAC for Q_2, TAC_{Q3}=TAC for Q_3, and TAC_{Q4}=TAC for Q_4, respectively. Q_1 denotes the upper right quadrant of the dentition; Q_2 denotes the upper left quadrant of the dentition; Q_3 denotes the lower left quadrant of the dentition; Q_4 denotes the lower right quadrant of the dentition.

Statistical Analysis

Descriptive statistics (mean and median values with ranges and frequency as counts and percentages) were used to describe the following features in persons with Apert or Crouzon syndrome:

- *General medical aspects* (gender, mental disability, ophthalmologic pathology, other associated malformations).
- *Craniofacial aspects* (facial profile, lip relationships and posture, cleft palate, bifid uvula, lateral palatal swellings).
- *Dentoalveolar traits* before and after the final orthognathic surgery (overjet, overbite, midline deviation, posterior crossbite, maxillary apical base).
- *Cranio-maxillofacial surgery* (types of surgical procedures and age when performed).
- *Dental agenesis* (excluding the third molars) and *dental agenesis patterns* (in the form of Tooth Agenesis Code) of permanent teeth.

The Confidence Interval Analysis (Wilson Test) was applied to compare variables between persons with Apert syndrome and persons with Crouzon syndrome, tested as proportions and their differences (Newcombe and Altman, 2000). These variables, with confidence intervals set to 95%, were related to:

- *General medical aspects* (gender, mental disability, associated additional malformations, ophthalmologic pathology).
- *Palatal characteristics* (isolated cleft palate, lateral palatal swellings).
- *Dentoalveolar traits* (bilateral mesial occlusion, negative overjet>6 mm, positive overjet<4 mm, openbite, overbite>4mm, lateral crossbite, midline deviation>3mm, small upper apical base).

The Fisher's Exact Test (Altman, 1991) was used to assess the prevalence of dental agenesis against gender. The Wilcoxon Signed-Rank Sum Test (Altman, 1991) was applied to evaluate differences in mean numbers of absent teeth between the left versus the right quadrant of the dentitions, and the maxillary versus the mandibular dentitions. Statistical significance was set at the 5% level.

Ethical Considerations

All studies were approved by the Regional Research Ethics Committee of Gothenburg (Registration Numbers Ö 342-99 and 149-08). All subjects were coded when entering each study and statistical analyses were carried out with unidentifiable data.

Summary: Type of study, topics of interest, data collection, data analysis

Study	*Study Type*	*Topics of Interest*	*Data Collection*	*Data Analysis*
I	Qualitative	Childhood, school situation, relations with friends and family in persons with Crouzon syndrome	• Open ended telephone interviews of persons with Crouzon syndrome 18 years old or older	• Grounded Theory
II	Qualitative	Daily life, thoughts about meeting a partner, friends, and thoughts about the future in persons with Crouzon syndrome		
III	Quantitative: Descriptive	The following features were investigated in persons with Apert or Crouzon syndrome: • *General medical aspects* (gender, mental disability, ophthalmologic pathology, other associated malformations) • *Craniofacial aspects* (facial profile, lip relationships and posture, cleft palate, bifid uvula, lateral palatal swellings) • *Dentoalveolar traits* before and after the final orthognathic surgery (overjet, overbite, midline deviation, posterior crossbite, maxillary apical base) • *Cranio-maxillofacial surgery* (types of surgical procedures and age when performed)	• Patient charts • Dental stone models before the final orthognathic surgery and after finished treatment	• Descriptive statistics (median values with ranges and frequency as counts and percentages) • Confidence Interval Analysis to test proportions and their differences (Wilson Test)
IV	Quantitative: Descriptive	Dental agenesis (excluding the 3rd molars) and dental agenesis patterns (in the form of Tooth Agenesis Code) of permanent teeth in Crouzon syndrome	• Panoramic radiographs • Patient charts	• Descriptive statistics (tooth counts and percentages) • Fisher's Exact Test • Wilcoxon Signed-Rank Sum Test
V	Quantitative: Descriptive	Dental agenesis (excluding the 3rd molars) and dental agenesis patterns (in the form of Tooth Agenesis Code) of permanent teeth in Apert syndrome		

Results

Study I: Living with Crouzon syndrome: Transition from childhood to adulthood.

It has been revealed, that persons with Crouzon syndrome, have had to face different obstacles when developing their self-image during the transition from childhood to adulthood. These findings were reflected in the core category of the study and were further analyzed in five descriptive categories (Figure 6).

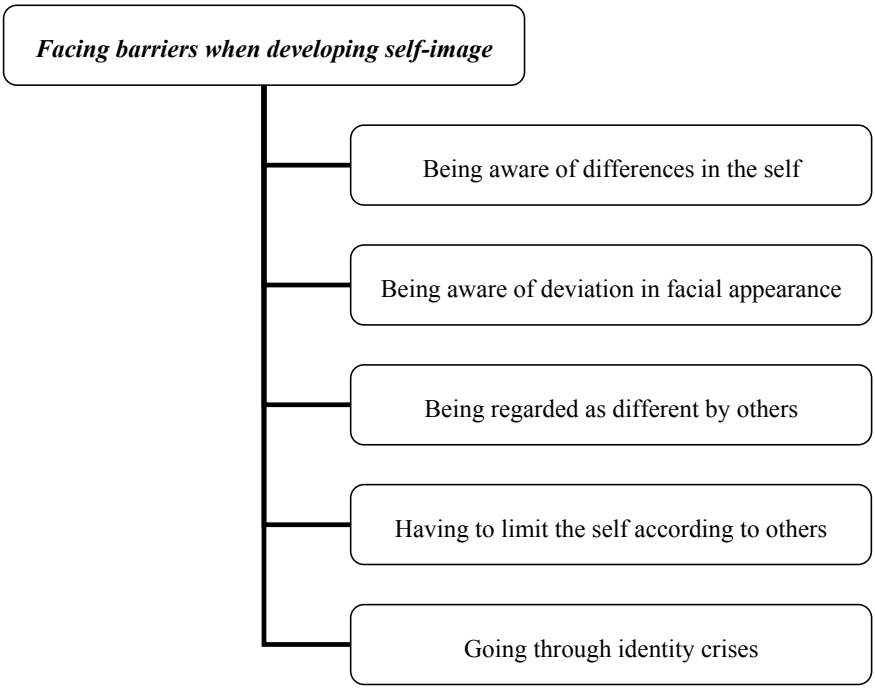

Figure 6. The relationship between the core category and the other categories identified from the interviews in Study I.

Children with Crouzon syndrome were exposed to several medical interventions to reduce complications related to craniosynostoses from a very early age. It seemed that they could not remember these early interventions. As such, during early childhood, children with Crouzon syndrome were not likely to be aware of their condition.

When they grew older and started to socialize with other children on a daily basis, they became aware of being different compared to other children. This was mainly due to the frequent hospital visits for medical examinations and treatments. Therefore, they were often absent from daycare centers, school, and friends. This seemed to be the first distinguishing difference between them and their peers. It can be described as a barrier for developing the self for the young child.

The interviewed persons with Crouzon syndrome also reported that they became aware of deviations in their facial appearance prior to, or during their first year in school. It was the first time that peers asked them about their facial features. During this process, they realized their facial disfigurement. This awareness was not necessarily experienced negatively in these early years.

Later on, the schoolmates of the children with Crouzon syndrome regarded them very often as different from others. This behavior, along with bullying and drawing of public attention, was experienced negatively from the disfigured children. It made them feel lonely and vulnerable.

Furthermore, the participants of the study described the overprotection they felt from their parents. Restrictions when playing rough games, continuous watching, and limited responsibilities hindered them from fully developing themselves. The more overprotective they felt, the less initiative they took in their lives. This in turn, resulted in more shyness and stress at times when they met new people.

The sudden and frequently dramatic changes, resulting from the cranio-maxillofacial surgical reconstructions the children with Crouzon syndrome experienced, also led to identity crises. This occurred particularly during the period of adolescence and led to insecurity and anxiety feelings. Returning to the school surroundings, where they had to present a new face, was felt as a very hard to cope with situation.

Study II: Living with Crouzon syndrome: How do young adults with Crouzon syndrome handle their life situation?

The main concern of the participants of the study, as described by the core category, was *to make the best of their situation*. In order to achieve this aim, they developed various strategies since childhood. These strategies, which helped them to handle their vulnerable life situation and enhance their well-being, were outlined in five descriptive categories (Figure 7).

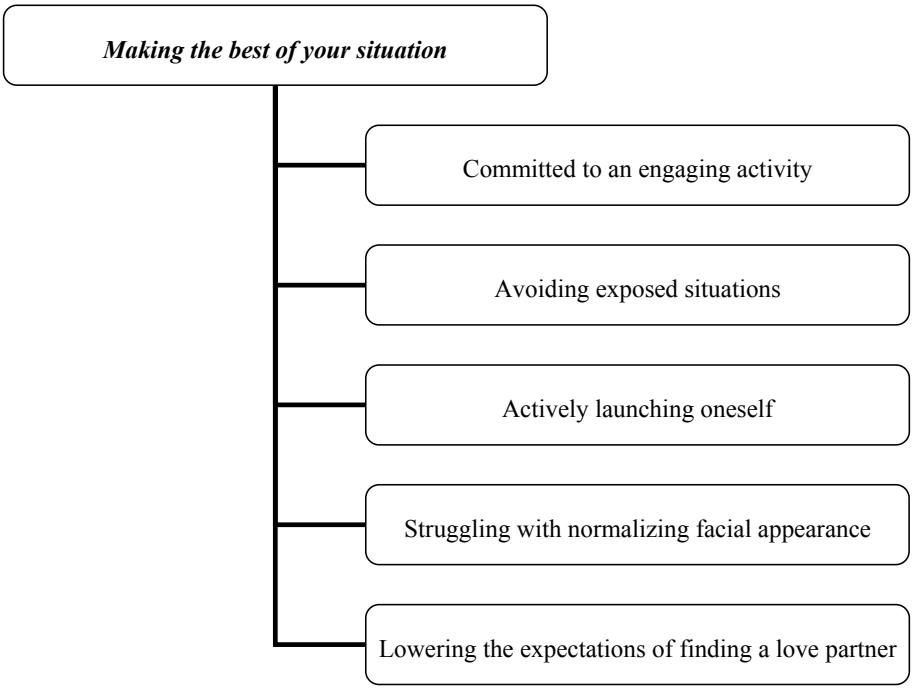

Figure 7. The relationship between the core category and the other categories identified from the interviews in Study II.

Commitment to an engaging and time-consuming interest helped the interviewed persons with Crouzon syndrome to feel less focused on their facial appearance. These interests, such as literature reading, engagement in the church or horseback riding, were described to be of such kind that the facial features did not matter.

The participants of the study also reported that they tried to avoid exposed situations, such as public places, where strangers could stare at them. Such unwelcomed attention was experienced as stressful. It made them think about their syndrome and feel as outsiders and less worthy than other people.

Furthermore, they carefully selected persons they wanted to be friends with. In this case, they actively launched themselves, trying to be social and humoristic. They wanted to help others to see behind the appearance of their face.

The interviewed individuals also described how much they struggled to normalize their appearance with several cranio-maxillofacial surgical reconstructions. The more they achieved to normalize their facial appearance, the better they felt. However, some of these surgeries were experienced as particularly

painful, both from a physical and a psychological point of view. Sometimes, the facial changes were dramatic, which in turn, led to identity crises. Moreover, frequent and lengthy hospitalizations distinguished them from their social environment and made them feel different.

Finally, under recognition that their facial appearance hindered them from finding a life partner, the participants of the study described that they lowered the choice of partner accordingly. They preferred to long for somebody who also suffered from an exposed life situation.

Study III: Comparing patients with Apert and Crouzon syndromes: Clinical features and cranio-maxillofacial surgical reconstruction.

General medical aspects

More females were registered in the Apert syndrome group than in the Crouzon syndrome group. Persons with Apert syndrome were found to display mental disability and associated additional malformations/deficits more frequently than persons with Crouzon syndrome (Figure 8).

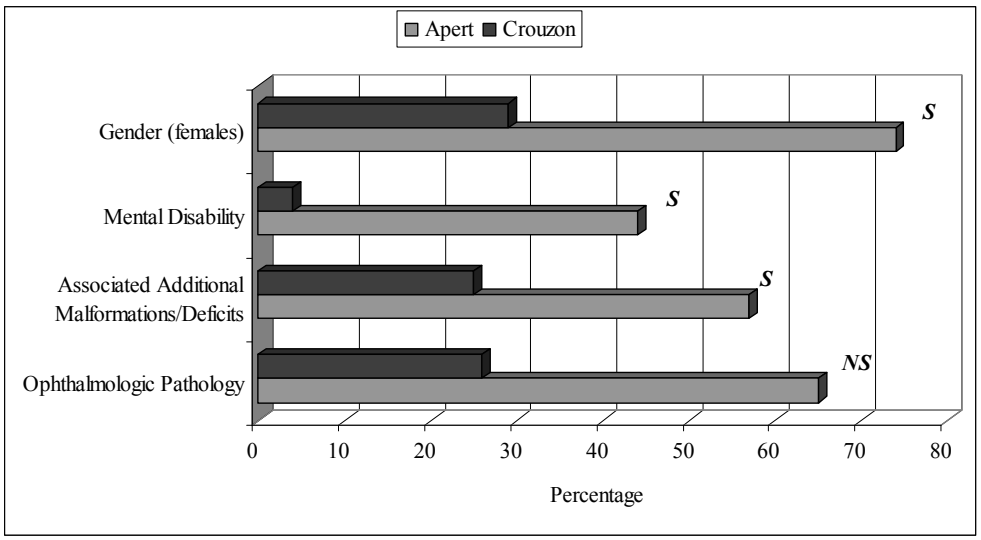

Figure 8. General medical variables compared between the Apert and the Crouzon syndrome study groups. S: Significant statistical difference; NS: Non-significant statistical difference.

The most frequent additional malformation/deficit registered for the Apert syndrome study group was mental disability, whereas for the Crouzon syndrome, it was hearing loss. Other malformations/deficits registered for both study groups involved deformed vertebrae, choanal atresia, temporomandibular dysfunction, malformed ears, back and body posture pathology, spinal cord scoliosis, aortal stenosis, heart pathology, urinary passage pathology.

Craniofacial aspects

The most frequent facial profile configuration observed was the concave for both study groups. About half of the persons with Apert syndrome exhibited a short and/or thin upper lip and a trapezoidal-shaped mouth. Most of the persons with Crouzon syndrome (71%) were assessed as having the lower lip protruded relatively to the upper.

About one fourth of the evaluated persons with Apert syndrome were registered with an isolated cleft palate, with two of these clefts being total and four being partial. Furthermore, in 22% of all the cases with Apert syndrome, a bifid uvula was identified. One person had a submucous palatal cleft. Extensive lateral palatal swellings were found in 78% of the whole Apert study group.

Persons with Crouzon syndrome did not exhibit cleft lip and/or palate. Figure 9 presents the main palatal features observed between the two study groups.

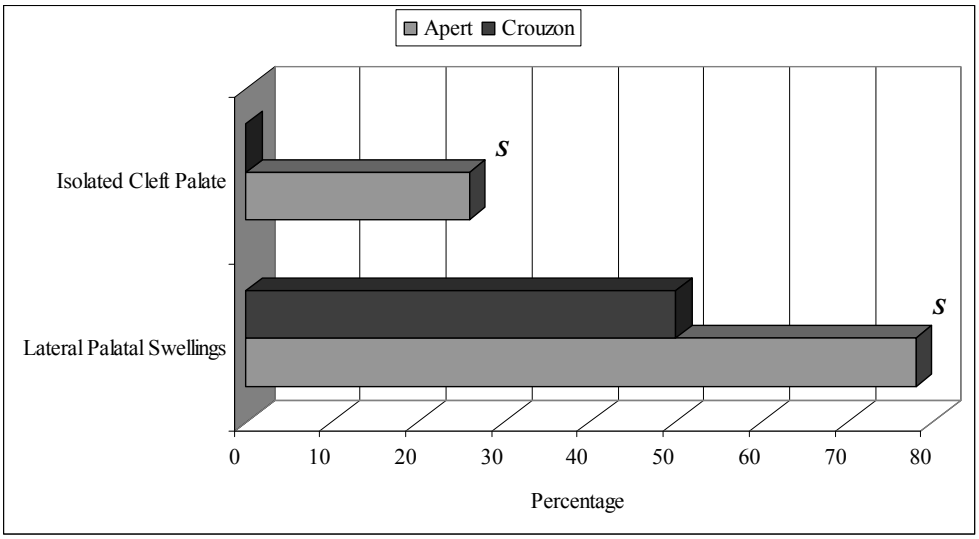

Figure 9. The main palatal features observed in the Apert and Crouzon syndrome study groups. S: Significant statistical difference.

Stone model analysis shortly before the final combined orthodontic and orthognathic surgery treatment

Bilateral molar mesial occlusion and midline deviation of more than 3 mm, were significantly more common in the recorded persons with Crouzon syndrome than in persons with Apert syndrome. Severe overjet, severe overbite, lateral crossbite and small upper apical base were frequent for both study groups, but there was no statistically significant difference observed between them (Figure 10).

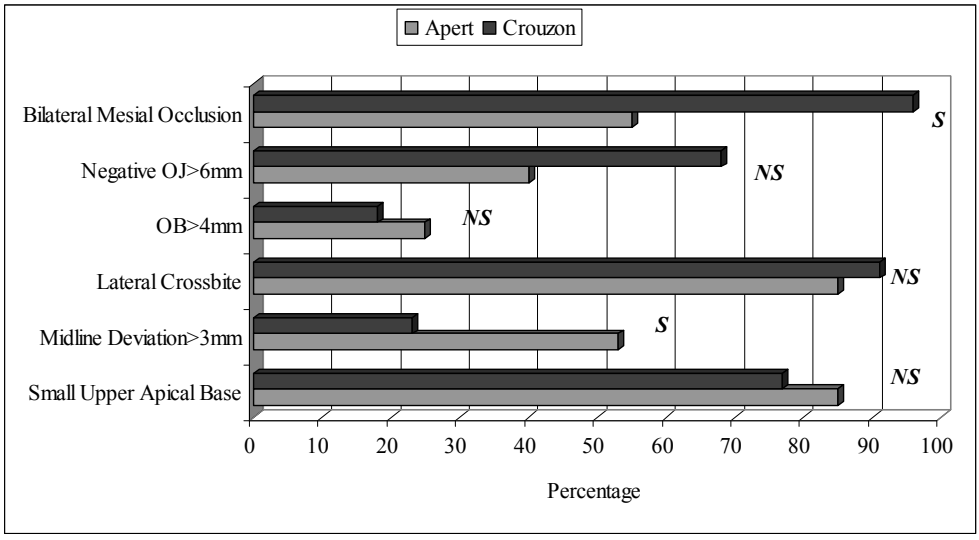

Figure 10. Stone model analysis shortly before the final combined orthodontic and orthognathic surgery treatment for the Apert and Crouzon syndrome study groups. OJ: Overjet; OB: Openbite; S: Significant statistical difference; NS: Non-significant statistical difference

Stone model analysis after the final combined orthodontic and orthognathic surgery treatment

Almost all of the persons registered for both study groups ended up with a positive overjet and overbite. A clear deviation of the dental midlines of more than three millimeters was observed in about one fifth of the cases in each group. A posterior crossbite was registered in about half of the persons with Apert or Crouzon syndrome. These results are further presented in Figure 11.

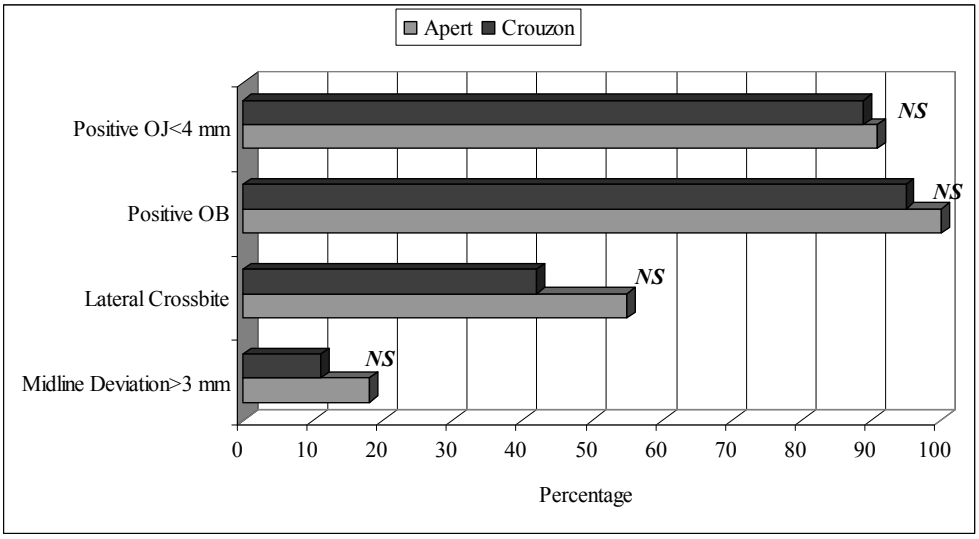

Figure 11. Stone model analysis shortly after the final combined orthodontic and orthognathic surgery treatment for the Apert and Crouzon syndrome study groups. OJ: Overjet; Positive OB: Positive overbite; NS: Non-significant statistical difference.

Cranio-maxillofacial surgery

During the first year of life, the majority of children with Apert syndrome (78%) or Crouzon syndrome (71%) had cranio-maxillofacial surgery performed. The most common operation was a cranial vault decompression and/or reshaping (CVR). The cranio-maxillofacial surgical sessions continued for 74% of the children with Apert syndrome and for 82% of the children with Crouzon syndrome between 1 to 12 years of age. The most frequent types of surgeries were CVR and midfacial advancement techniques. Between 12 to 16 years of age, 35% of teenagers with Apert syndrome and 42% of teenagers with Crouzon syndrome experienced at least an additional surgery in the craniofacial region, mainly a midfacial advancement operation. A session of final orthognathic surgery was carried out for half of the patients with Apert syndrome and almost all of the patients with Crouzon syndrome (91%). Le Fort I maxillary advancement osteotomies, often combined with mandibular set-back osteotomies, were the most frequent surgical procedures.

Study IV: Dental agenesis patterns in Crouzon syndrome.
Study V: Dental agenesis patterns of permanent teeth in Apert syndrome.

Dental agenesis prevalence

Eleven out of 26 (42.3%) persons with Crouzon syndrome were identified to exhibit dental agenesis. Seven (26.9%) were missing one tooth only. Four (15.4%) were observed missing two teeth or more.

Eight out of 23 (34.8%) persons with Apert syndrome were found to exhibit dental agenesis. One individual (4.4%) was missing one tooth only. Seven (30.4%) were missing two teeth.

Figure 12 presents the prevalence of dental agenesis observed in the two study groups.

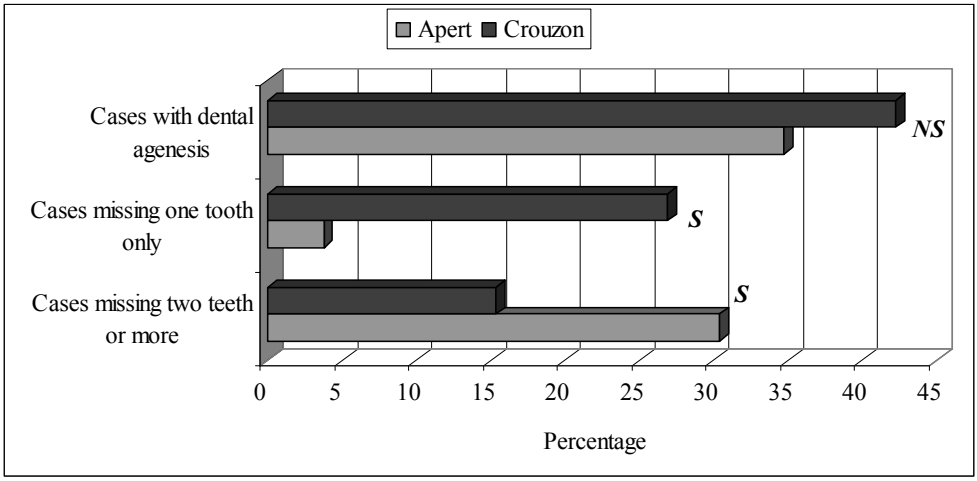

Figure 12. Prevalence of dental agenesis in the Crouzon and Apert study groups. S: Significant statistical difference; NS: Non-significant statistical difference.

The most frequently missing teeth identified in persons with Crouzon syndrome were the mandibular and maxillary second premolars, followed by mandibular central incisors and maxillary second molars. Persons with Apert syndrome were found to be missing mandibular second premolars and maxillary lateral incisors more frequently. Tables 3 and 4 present the prevalence of dental

agenesis per tooth type in the studied populations with Crouzon or Apert syndrome, respectively.

Table 3

Prevalence of dental agenesis per tooth type, for each quadrant of the dentition in 26 individuals with Crouzon syndrome

Q1							***Q2***						
7.6% n=2	0% n=0	15.3% n=4	0% n=0	0% n=0	3.8% n=1	0% n=0	0% n=0	0% n=0	0% n=0	0% n=0	7.6% n=2	3.8% n=1	7.6% n=2
M_2	M_1	P_2	P_1	Ca	I_2	I_1	I_1	I_2	Ca	P_1	P_2	M_1	M_2
0% n=0	0% n=0	11.5% n=3	0% n=0	0% n=0	0% n=0	7.6% n=2	7.6% n=2	0% n=0	0% n=0	0% n=0	11.5% n=3	0% n=0	0% n=0
Q4							***Q3***						

n: Number of absent teeth. Q_1, Q_2, Q_3, Q_4: First to fourth quadrant of the dentition. In grey: Tooth type. M_2: Second molar; M_1: First molar; P_2: Second premolar; P_1: First premolar; Ca: Canine; I_2: Lateral incisor; I_1: Central incisor. Third molars were not included in the assessment.

Table 4

Prevalence of dental agenesis per tooth type, for each quadrant of the dentition in 23 individuals with Apert syndrome

Q1							***Q2***						
0% n=0	0% n=0	0% n=0	4.3% n=1	0% n=0	13% n=3	0% n=0	0% n=0	17.3% n=4	0% n=0	4.3% n=1	0% n=0	0% n=0	0% n=0
M_2	M_1	P_2	P_1	Ca	I_2	I_1	I_1	I_2	Ca	P_1	P_2	M_1	M_2
0% n=0	0% n=0	13% n=3	0% n=0	0% n=0	0% n=0	0% n=0	0% n=0	0% n=0	0% n=0	0% n=0	13% n=3	0% n=0	0% n=0
Q4							***Q3***						

n: Number of absent teeth. Q_1, Q_2, Q_3, Q_4: First to fourth quadrant of the dentition. In grey: Tooth type. M_2: Second molar; M_1: First molar; P_2: Second premolar; P_1: First premolar; Ca: Canine; I_2: Lateral incisor; I_1: Central incisor. Third molars were not included in the assessment.

There was no statistically significant difference observed between prevalence of dental agenesis and gender in each of the two study groups (p=0.179 for the Crouzon study group; p=1 for the Apert study group). No statistically significant difference was identified in the number of missing teeth between the maxillary

versus the mandibular dentitions for each of the two study populations (p=0.405 for the Crouzon study group; p=0.651 for the Apert study group). Neither was any statistically significant difference found in the number of congenitally absent teeth between the left versus the right quadrants of the dentitions for the Crouzon (p=0.593) or the Apert (p=0.317) study groups.

Dental agenesis patterns

All of the eleven dental agenesis patterns identified for the entire dentition for persons with Crouzon syndrome were unique (Table 5). There were also asymmetrical patterns, with only one exception of a symmetrical pattern, of maxillary and mandibular second premolars at the right side of the dentition of one person. This pattern was described by the $TAC_{overall}$ score of 16.0.0.16, involving the teeth 15, 45.

Table 5

$TAC_{overall}$ score, corresponding absent teeth, frequency and percentage of each $TAC_{overall}$ score for the 26 persons with Crouzon syndrome studied

$TAC_{overall}$*	***Absent teeth***	***Frequency***	***Percentage***
0.0.0.0	none	15	57.6
16.0.0.0	15	1	3.8
2.0.0.0	12	1	3.8
0.64.0.0	27	1	3.8
0.32.0.0	26	1	3.8
64.0.0.0	17	1	3.8
0.0.0.16	45	1	3.8
0.0.16.0	35	1	3.8
16.0.0.16	15, 45	1	3.8
0.0.17.1	35, 31, 41	1	3.8
16.80.16.16	15, 25, 27, 35, 45	1	3.8
80.16.1.1	17, 15, 25, 31, 41	1	3.8
Total		26	100

*Third molars were not included in the assessment.
$TAC_{overall}$: Tooth Agenesis Code for the entire mouth.

Four distinct dental agenesis patterns were identified for the entire dentition for persons with Apert syndrome (Table 6). Two of these patterns were found to be repetitive (occurring three times each). They were described by the $TAC_{overall}$ scores

of 2.2.0.0 (involving the teeth 12, 22) and 0.0.16.16 (involving the teeth 35, 45). All of the dental agenesis patterns which showed more than one tooth missing were observed to be symmetrical.

Table 6

$TAC_{overall}$ score, corresponding absent teeth, frequency and percentage of each $TAC_{overall}$ score for the 23 persons with Apert syndrome studied

$TAC_{overall}$ [*]	***Absent teeth***	***Frequency***	***Percentage***
0.0.0.0	none	15	65.2
2.2.0.0	12, 22	3	13.0
0.2.0.0	22	1	4.3
0.0.16.16	35, 45	3	13.0
8.8.0.0	14, 24	1	4.3
Total		23	100

[*]Third molars were not included in the assessment.
$TAC_{overall}$: Tooth Agenesis Code for the entire mouth. In grey: Repetitive dental agenesis patterns.

Discussion

The Apert and Crouzon syndrome research project started with two qualitative interview studies (Studies I and II) in order to gain knowledge about the subjective feelings of persons born with these syndromes. Such methodology is particularly useful for exploring rare and under-studied social processes (Hallberg, 2006). Persons with severe health problems, such as mental disability and acute hearing problems, were not able to participate in these two studies. The next step was to conduct a descriptive study on the clinical features of the two syndromes, as well as on the cranio-maxillofacial surgical treatment protocols followed (Study III). Finally, dental agenesis and dental agenesis patterns of permanent teeth were investigated (Studies IV and V). Therefore, the research strategy followed in this thesis dealt with the more general and subjective aspects initially, with subsequent focus on more specific and objectively assessed features.

The development of the self-image during the transition from childhood to adulthood in children with Crouzon syndrome (Study I)

Persons with Crouzon syndrome faced several stressful obstacles, which they had to cope with, when developing their self-image during the transition from childhood to adulthood. The very obvious craniofacial stigmata, along with possible functional problems, were probably the main reasons behind the obstacles experienced by these patients. Reports on children with severe craniofacial deformities (Pruzinsky, 1992) or with chronic physical illness (Wallander et al., 1988), point out that these children experience many psychological stress factors to which they have to learn to adapt and which may affect their psychological development.

A facial disfigurement during growth and development may be seen as an adverse situation. This may be due to the self not been fully developed during the transition from childhood to adulthood. Its formation is largely based on confirmation received from others (Jourard, 1963). Stigma may result in shame and self-image shattering, and the stigmatized have to learn to live in a society where they are not considered complete and are often segregated.

Children with Crouzon syndrome felt different when they compared themselves to others, as it was denoted in the descriptive categories of Study I "being aware of differences in the self", "being aware of deviation in the facial appearance", and "being regarded as different by others". This observation of feeling different is in line with similar findings in a qualitative investigation in

young adults with cleft lip and palate (Chetpakdeechit et al., 2009). Children start to judge physical attractiveness in peers during the first years of school (Bull and Rumsey, 1988). There is evidence that children around 7-8 years of age start to form their cognition according to their own preferences (Kalish and Shiverick, 2004), form stereotypes and show stigmatizing behaviors (Hearst, 2007). In fact, this process may even start earlier (Miller and Aloise, 1989; Eder, 1995).

Parental overprotection was an additional obstacle which children with Crouzon syndrome had to face during the development of their self. This was coherently described in the category "having to limit the self according to others". Overprotection implies behaviors beyond what most parents with healthy children would do in similar circumstances (Thomasgard and Metz, 1993). Although well-intentioned, the overprotective parent may adversely affect the child's drive for autonomy and self-actualization (Mahoney, 1988). This, in turn, may undermine the child's social skills (Speltz et al., 1994).

Identity crises constituted another impediment that the interviewed persons in Study I had to overcome in their effort to develop their self. Such episodes of crisis were attributed partly to the sudden and sometimes profound changes produced by the cranio-maxillofacial surgical reconstructions, which placed immediate demands on the adaptive skills of the patient. This is in line with findings which point out that a young person's attempt to integrate his/her facial image into a stable identity and overall body scheme, may be compromised when facial appearance is likely to change radically with surgery (Hearst, 2007). Orthognathic surgery patients have been found to need up to two years to accept, as permanent, the effects of facial change in their personality (Kiyak et al., 1984).

How young adults with Crouzon syndrome handle their life (Study II)

The qualitative study revealed a core category "making the best of your situation", showing that even in adverse conditions, as in Crouzon syndrome, some individuals may find ways to succeed in various aspects of life using several strategies. This is in line with findings which point out that in people with craniofacial anomalies, despite numerous challenges, healing may occur and they may join non-affected persons in the search of meaning and quality in their lives (Strauss and Fenson, 2005). This process may be described as "normal development under difficult conditions" (Fonagy et al., 1994). It involves both risks and protective processes that an individual may apply, and which act to modify the effects of an adverse life event (Rutter, 1985).

Commitment to an engaging activity, where facial appearance did not matter, was one of the coping strategies that persons with Crouzon syndrome used to handle their vulnerable life situation. Horseback riding was cited as such an activity

by the interviewed persons in Study II. Inner spiritual strength, religious beliefs and faith have also been reported as important sources of comfort and meaning (Strauss and Fenson, 2005).

An additional coping strategy, identified in Study II, was described as "avoiding exposed situations", related to the protection of the self (Lazarus, 1993). Another one was described as "actively launching oneself", related to the presentation of the self (Thompson and Kent, 2001). These coping strategies reflect the behaviors that the interviewed persons employed, in order to cope with their lives.

Improving the facial appearance with the help of surgery was an important task for persons with Crouzon syndrome. This was described in the category "struggling with normalizing facial appearance". A similar attitude expressed by a core category "hoping to be like other people" has been observed in a recent qualitative study in patients with cleft lip and palate (Chetpakdeechit et al., 2009). However, it has been described that sometimes care providers are colluding with the myth that the quality of life necessarily improves when physical appearance is enhanced (Rumsey and Harcourt, 2004). For some people, one operation may be enough, but many undergo a series of surgeries in the quest for a "normal" appearance. The patients' own perspective should be highly considered, since their understanding of treatment improvement may differ fundamentally from the clinicians or their parents (Turner et al., 1997).

"Lowering the expectations of finding a love partner" was also a strategy that persons with Crouzon syndrome used in order to handle their life situation. More than 70% of individuals with craniofacial anomalies felt that others did not want to become romantically involved with them due to their appearance (Sarwer et al., 1999).

Gender predilection in Apert and Crouzon syndromes (Study III)

More females were observed to have Apert syndrome and more males were identified to have Crouzon syndrome in the studied groups. One reason for this finding may be the small sample sizes of the groups. In population-based samples, no gender predilection has been found for Apert syndrome (Cohen and Kreiborg, 1991; Tolarova et al., 1997). However, in a subsample of a study population that was collected from a craniofacial center in San Francisco, California, a clear female dominance has been observed for Apert syndrome (Tolarova et al., 1997).

In a comprehensive study on Crouzon syndrome, a slight higher male proportion (54% of males) has been found (Kreiborg and Pruzansky, 1981). This difference may be considered generally in line with the findings of Study III.

Additional malformations/deficits that persons with Apert or Crouzon syndrome suffer from (Study III)

Additional malformations/deficits were frequent for the two syndromes studied, with a higher frequency for Apert syndrome. This finding is in line with other literature sources (Cohen, 2000b). These malformations/deficits were not restricted to the craniofacial region, implying a pleiotropic activity of the *FGFR* gene.

The mental capacity of persons with Apert or Crouzon syndromes is an important issue. About half of the patients with Apert syndrome in Study III had a recorded mental disability. This is consistent with literature reports (Patton et al., 1988; Renier et al., 1996) and may be attributed to several central nervous system abnormalities these patients can have (Cohen and Kreiborg, 1990). Fine motor deficits due to the syndactyly, or low language skills due to cleft palate, may also explain their low scores in IQ performance tests (Shipster et al., 2002). The vast majority of persons with Crouzon syndrome (96% in study III) were recorded with a mental capacity within normal range. This is in line with similar research findings in literature (Kreiborg and Pruzansky, 1981).

Facial profile in Apert and Crouzon syndromes (Study III)

In both syndromes, the facial profile was assessed as concave in the majority of the cases. This is attributed to the midfacial hypoplasia, which is a cardinal clinical feature of these syndromes (Cohen, 2000b).

In the Crouzon syndrome sample, the lower lip posture was assessed mostly as protruded. This clinical expression can be explained on the basis of the relative mandibular prognathism persons with Crouzon syndrome have, due to the hypoplastic maxilla. The upper lip posture in the Apert syndrome study group was evaluated as short and/or thin in about half of the cases. The reason for this observation may not only be the maxillary hypoplasia in the sagittal plane. It may also be the hypoplastic anterior cranial base, postulated as the primary craniofacial abnormality, in persons with Apert syndrome (Kreiborg et al., 1993), which further restricts the normal vertical and forward growth and/or displacement of the maxilla. This may result in a higher position of the upper lip and is also consistent with the finding of Study III, that an anterior openbite was much more common in the Apert syndrome study group.

Oral features in Apert and Crouzon syndromes (Study III)

The palatal morphology in Apert syndrome is of special interest. Bifid uvula, cleft palate and extensive lateral palatal swellings (containing muccopolysacharides) were more frequent in the studied group with Apert syndrome than in that with Crouzon syndrome. These findings are in line with current literature sources (Cohen, 2000b). The reported prevalence of cleft palate in Apert syndrome varies from 4% (Letra et al., 2007) to 11% (Peterson and Pruzansky, 1974), and up to as high as 41% (Kreiborg and Cohen, 1992). Racial and ethnic differences among the investigated samples may be a reason for these large variations.

Several malocclusion features were registered as common for both the Apert and Crouzon syndrome groups. These included negative overjet, anterior openbite, and posterior crossbites. The deficient maxillary growth in all planes of space (Kreiborg and Pruzansky, 1981) may be the main reason for these observations. Bilateral mesial occlusion on the first permanent molars was found to be less common in Apert than in Crouzon syndrome. A possible explanation may be the high severity of crowding that these patients show in the lateral segments of the maxilla, which can lead to premature loss of maxillary primary molars and/or ectopic eruption of permanent premolars, with resultant mesial migration of the permanent maxillary molars (Kreiborg and Cohen, 1992). This process, along with the frequently encountered asymmetric Apert cranial base (Kreiborg et al., 1993), may also explain the more frequent registration of dental midline deviation in the Apert syndrome study group compared to the Crouzon syndrome study group.

Dental crowding was not evaluated in the present research project, due to orthodontic interventions and dental extractions that had been performed at various ages.

Following the final orthodontic and orthognathic surgery treatment session, the most of the malocclusion features were significantly improved in almost all cases of both syndrome groups. However, the posterior crossbites were observed to be persisting in almost half of the cases in each study group. Nevertheless, it is worth to be noted that recent research indicates that negative functional consequences from crossbites are rarely evidenced (Mohlin et al., 2007).

Cranio-maxillofacial surgery (Study III)

The patients with Apert or Crouzon syndromes underwent a series of cranio-maxillofacial surgeries, even from an infantile age, in order to improve cranial and facial growth and development. Among later surgeries, multiple midfacial advancements with several surgical techniques were common. A Le Fort III facial

advancement, as well as orbital advancement were the most usual operations. Routinely nowadays, implantable metal springs pushing forward were used to counteract the soft tissue forces that follow midfacial forward repositioning (Lauritzen et al., 2008). After growth completion, a final orthognathic surgical approach in these patients was performed (Kahnberg and Hagberg, 2010). This was most often a Le Fort I maxillary advancement, frequently combined with a mandibular set-back osteotomy.

One reason for the repetitive midfacial operations is that they were done in an effort to counteract the progressive craniofacial growth deficiency, which is inherent in these syndromes. However, midfacial growth still remains deficient after the surgical sessions and cannot keep pace with mandibular growth; the defective function of the *FGFR2* gene continues throughout the whole growth period of the children with the syndromes. Thus, even if there is a temporary improvement in craniofacial morphology after the surgical sutural release, the recurrence of synostosis may be a matter of time (Friede et al., 1983). Another reason for the multiple cranio-maxillofacial surgeries may be the surrounding soft tissue envelope which limits the surgical advancement of the facial bony structures. As such, repeated procedures for adequate advancement of the craniofacial skeleton, were necessary (Perlyn et al., 2009). Furthermore, Apert and Crouzon syndromes constitute complex surgical challenges that require a stepwise approach in several instances in order to avoid possible frequent and severe infections when great mobilizations of the craniofacial skeleton are made (Marchac and Renier, 1996).

Therefore, it is not surprising that more and more frequently, statements are appearing in the literature postulating that surgical treatments in genetically determined craniosynostosis seem like "treating a molecular disease with a hammer and chisel", producing esthetic outcomes less than optimal (Perlyn et al., 2009). Consequently, research has started focusing on pharmacologic compounds that attenuate the abnormal molecular signaling in order to prevent suture fusion on Apert syndrome (Shukla et al., 2007) as well as on Crouzon syndrome (Eswarakumar et al., 2006; Perlyn et al., 2006) in animal models.

Dental agenesis of permanent teeth in Crouzon syndrome (Study IV) and in Apert syndrome (Study V)

Excluding the third molars, dental agenesis was observed to be high in the studied populations with Crouzon syndrome (42.3%) and Apert syndrome (34.8%). The rates for the general population have been reported to range between 3.2% to 7.6% in a recent meta-analysis study (Polder et al., 2004) and between 6.1% to 7.4% in studies in Swedish samples (Thilander and Myrberg, 1973; Bergstrom, 1977;

Backman and Wahlin, 2001). Investigations in Apert syndrome study groups have observed dental agenesis as high as 41% to 44.4% (Dalben Gda et al., 2006b; Letra et al., 2007). However, in an investigation in a Crouzon syndrome sample, only 5 dental agenesis cases were reported of the 61 that were evaluated (Kreiborg and Pruzansky, 1981). This cited study did not have the identification of dental agenesis among its primary aims. This is an important issue under recognition that dental agenesis seems to be underestimated when it is one of the multiple aims of a big research project (Polder et al., 2004).

The high prevalence of dental agenesis in the studied groups may be explained by the common developmental pathways that teeth and orofacial structures recruit during morphogenesis, growth, and development of the craniofacial region (Matalova et al., 2008). The mutated *FGFR2* gene, causative for Crouzon or Apert syndrome, may also be involved in the pathogenesis of dental agenesis. This is since the signaling molecules that bind to FGFRs, the FGFs, have been observed to be expressed during all stages of dental morphogenesis (Thesleff, 1998). Thus, failure in the function of FGFs in the dental epithelium and/or in the underlying mesenchyme and their receptors (the FGFRs) during tooth development, may result in dental agenesis (De Coster et al., 2009). Experimental research indicated that inactivation of the *FGFR2* gene in the dental epithelium in mice, led to cessation of mandibular first molar development at the cap stage (Kettunen et al., 2007). Another study in mice showed that an *FGFR2* gene mutation produced, among other effects, agenesis of the tooth bud (Revest et al., 2001).

An equal prevalence rate was found for both genders regarding dental agenesis for the Crouzon as well as the Apert studied groups. This is in contrast to reports in the general population, which indicate a higher prevalence of dental agenesis in females (Polder et al., 2004; Larmour et al., 2005; Creton et al., 2007). Investigations in the Swedish general population samples show varying results. Some studies have showed no gender predilection in dental agenesis (Thilander and Myrberg, 1973; Backman and Wahlin, 2001), whereas another report has concluded that there is a female to male ratio of 3:2 (Bergstrom, 1977). The relative small sample sizes of Studies IV and V may not allow the drawing of definite conclusions in this matter.

Most cases of dental agenesis in the Crouzon syndrome study group were unilateral, involving one tooth only, usually a maxillary or a mandibular second premolar. In the Apert syndrome study group, most of the dental agenesis cases were bilateral, with mandibular second premolars and lateral incisors predominantly affected. Research in the general population has indicated unilateral agenesis as more frequent (Polder et al., 2004). In studies in non-syndromic forms of dental agenesis in Caucasian populations, the mandibular second premolar has been the most frequently missing tooth, followed by the maxillary lateral incisor and the maxillary second premolar (Thilander and Myrberg, 1973; Polder et al.,

2004). However, in Asian populations, the most commonly affected tooth has been reported to be the mandibular incisor (Davis, 1987), or the maxillary lateral incisor (Nik-Hussein, 1989). The reported results reflect a variability in sub-populations.

All dental agenesis patterns of the entire mouth identified in the Crouzon syndrome study group were unique, in terms of being observed only once. Furthermore, they were also found to be asymmetrical, with the only exception of the pattern with a $TAC_{overall}$ score of 16.0.0.16 (agenesis of 15, 45). Such dental phenotypic variability may go hand in hand with the craniofacial phenotypic variability of this syndrome, ranging from very mild to very severe. This may be explained by the genetic heterogeneity of the syndrome, since over 30 different *FGFR* gene mutations have been reported causative to Crouzon syndrome (Bonaventure and El Ghouzzi, 2003). Unexpectedly, identical *FGFR2* mutations affecting cysteines 278 and 342 have been found to cause both Pfeiffer and Crouzon syndromes (Rutland et al., 1995). Thus, possible epistatic gene expressions have been implied, that may interfere with the phenotypic expression of these conditions and may account for some of the variability observed.

Almost all the dental agenesis patterns of the entire mouth that were identified in the Apert syndrome study group were symmetrical. Two of them were repetitive, one involving the absence of the maxillary lateral incisors ($TAC_{overall}$ score of 2.2.0.0) and one the absence of the mandibular second premolars ($TAC_{overall}$ score of 0.0.16.16). The limited variability in dental agenesis patterns observed in Study V is a finding in accordance with the limited genetic variability which characterizes Apert syndrome. In a study where 260 patients with Apert syndrome were analyzed, 99% of them had one of two different point mutations (Ser252Trp and Pro253Arg) in exon 7 of the *FGFR2* gene (Oldridge et al., 1999). The possible correlation between these mutations to the 2.2.0.0 and the 0.0.16.16 dental agenesis patterns may be considered an interesting hypothesis for future research in patients with Apert syndrome. Genotype-phenotype correlations in these persons have already been found. For instance, it has been reported that the Pro253Arg mutation was more frequently present with a more severe degree of syndactyly, whereas the Ser252Trp mutation was associated with increased craniofacial defects, such as cleft palate (Slaney et al., 1996).

Methodological aspects (Studies I-V)

For decades, the GCC has been the solitary national reference center for treatment of craniofacial anomalies in Sweden. As such, the studied samples of persons with Apert or Crouzon syndromes may be seen as total samples of persons with these syndromes in Sweden, collected during a period of about 30 years. Since these two conditions have very low birth prevalence, the study groups of the present research

project may be considered as small. However, sufficient enough in order to produce significant findings. Future multi-center studies are needed to further increase knowledge on the issues in this thesis.

The craniofacial team at GCC consists of a multidisciplinary team which continuously over years registered systematically the craniofacial development, the growth of the jaws, and the development of the dentition of these patients. The team was led by the same craniofacial surgeon and the same maxillofacial surgeon, throughout the years covered by this research project. The orthodontic treatment was planned and followed up by an orthodontist specialized in treating syndromes. When the patient lived far away from the region of Gothenburg, the local orthodontist treated the patient in collaboration with the team.

Living with Crouzon syndrome (Studies I and II) is a social process that has been poorly described to date. A qualitative methodology was employed to investigate this process. It is frequently used when the object of study concerns human beings and their participation in society. "Qualitative" refers to quality in the properties (e.g., character, complexity, nature) that define the phenomenon under study. Such methodology aims to identify new questions regarding a research topic rather than to give definite answers, and to understand social processes rather than explain (Malterud, 2001). Therefore, qualitative research may be viewed as hypothesis generating, valuable at providing new information on unexplored research areas. Future quantitative research can complement qualitative research findings in order to strengthen the validity of clinical evidence.

Grounded Theory was the qualitative method employed to investigate living with Crouzon syndrome. It is especially suitable when studying how people handle or behave in a special situation (Glaser, 1998). Furthermore, a theory/hypothesis identified through this research process is grounded in the data obtained, for instance from interviews, as is the case in the present thesis. Data collection and analysis proceed at the same time until new interviews bring no more new information; thereby, *saturation* is said to be reached (Charmaz, 2000). Thus, it may be stated that Grounded Theory includes a form of testing the emerging theory/hypothesis, which is unique in qualitative research.

The limitations of the qualitative Studies I and II should also be considered. Firstly, telephone interviews were preferred because of issues, such as long distances between the participants and the interviewer, or work commitment of some participants. This was done at the expense of potentially missing some aspects of non-verbal communication. Nevertheless, this process was assessed to help in creating a neutral environment for the interviews. Secondly, the possibility for an ascertainment bias in the persons who were recruited for the interviews may not be excluded. Crouzon syndrome shows variable clinical severity; thus, less outgoing persons with the syndrome may not have been able to participate in the investigation. Persons with Apert syndrome did not accept to be included in the

interviews for a separate study, possibly due to severe health problems, such as mental disability and acute hearing problems. Most of the studies that deal with psychosocial issues on people with craniofacial syndromes are not homogeneous. The study populations include several syndromes. Consequently, limitations in validity issues in these studies arise. Finally, due to the low prevalence of Crouzon syndrome, the number of participants in the interviews was rather limited. Therefore, although the saturation in the qualitative studies was believed to have been reached, the produced results may be seen as tentative. However, in grounded theory studies, the unit of analysis concerns *events* and *stories* rather than the participants per se (Charmaz, 2000). Thus, the content and the quality of data are more interesting than the number of participants.

The sample size in Study III was reduced progressively with patients' age. This was since some of the participants in the study had not completed growth in order to initiate the final treatment stage with combined orthodontics and orthognathic surgery. Some of them were also under pre-surgical orthodontic treatment, waiting for the orthognathic surgery to be performed.

In order to prevent misdiagnosis of dental agenesis in Studies IV and V, special attention was given to the second premolars, reported to show late mineralization in 10-year old children in the general population (Cunat and Collord, 1973). Furthermore, children with Apert syndrome have been observed to show a mean dental developmental delay of 0.97 years between 7 to 10 years old (Kaloust et al., 1997). Thus, a panoramic radiograph from at least 11 years of age had to be available before a diagnosis of agenesis of second premolars was set.

Clinical implications (Studies I-V)

Concerns about physical appearance are highly increased during adolescence and young adulthood. As such, persons with Crouzon syndrome, who also carry the load of their condition, may have particularly tough experiences at this time. Understanding the patients' views and concerns is central to contemporary health care services. Knowledge about the special psychosocial profiles of persons with Crouzon syndrome may help providers of health care services for these patients to further develop their work and enhance the patients' satisfaction.

Some of the stressful obstacles that people with Crouzon syndrome face when developing their self-image during the transition from childhood to adulthood are related to the degree of social acceptance of facial disfigurement. Therefore, the habilitation of this group of people should also focus beyond medical and psychological treatment modalities, on public health interventions for reducing discrimination related to facial differences. Health care interventions for these

people should not just manage the pathological conditions, but also promote adaptive coping strategies, aimed at enhancing their well-being.

Frequent additional malformations/deficits were noted for both syndromes. Therefore, early and thorough general medical screening tests, are suggested for these persons. This will help in early diagnosis and better management of several pathologic situations that come along with these syndromes.

Knowledge about the development of the occlusion over years and the high prevalence of dental agenesis in persons with Apert or Crouzon syndrome is of great interest for dental practitioners. The clinical situation should be carefully considered, especially since orthodontic treatment planning for these patients starts as early as in the period of the mixed dentition.

Dental agenesis patterns may prove a useful tool for subphenotyping persons with Apert or Crouzon syndrome. Possible future genotype-phenotype correlations on this clinical aspect may shed more light on the molecular pathways that regulate these conditions.

The use of a common coding system, as the TAC, which describes dental agenesis, may be helpful for facilitating direct comparisons among various population samples. It may also ease the performance of meta-analyses on tooth agenesis, thereby strengthening the evidence on various aspects of this clinical condition.

Conclusions

- "Facing barriers when developing self-image" during the transition from childhood to adulthood was the core (main) category when persons with Crouzon syndrome were interviewed using the qualitative method of "Grounded Theory" (Study I).
- "Making the best of your situation" was the main concern for young adults with Crouzon syndrome in transition to adult life when they were interviewed using this qualitative method (Study II).
- Some individuals with Crouzon syndrome may find ways to enhance their life's well-being using specific strategies, as for example, commitment to an engaging activity (Study II).
- Apert syndrome is a more severe condition than Crouzon syndrome with a higher prevalence of mental disability (Study III).
- Negative overjet, marked openbite, lateral crossbite, and dental midline deviation were common dentoalveolar findings in persons with Apert or Crouzon syndrome. Apert syndrome presented more often midline deviations (Study III).
- Syndromic dentoalveolar characteristics of both syndromes were improved after a series of cranio-maxillofacial operations. However, lateral crossbites often persisted (Study III).
- The persons with Crouzon syndrome were found to have a high prevalence of dental agenesis. The most frequently missing teeth were the mandibular and maxillary second premolars. Almost all of the dental agenesis patterns showed asymmetry and a remarkable variability (Study IV).
- The individuals with Apert syndrome were observed to exhibit a high prevalence of dental agenesis. The most frequently missing teeth were the mandibular second premolars and maxillary lateral incisors. All of the dental agenesis patterns which were missing more than one tooth were symmetrical (Study V).

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