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FGFR2 gene related Apert and Crouzon Syndrome with Different Craniofacial Dysmorphism: A Systematic Review and Meta-analysis

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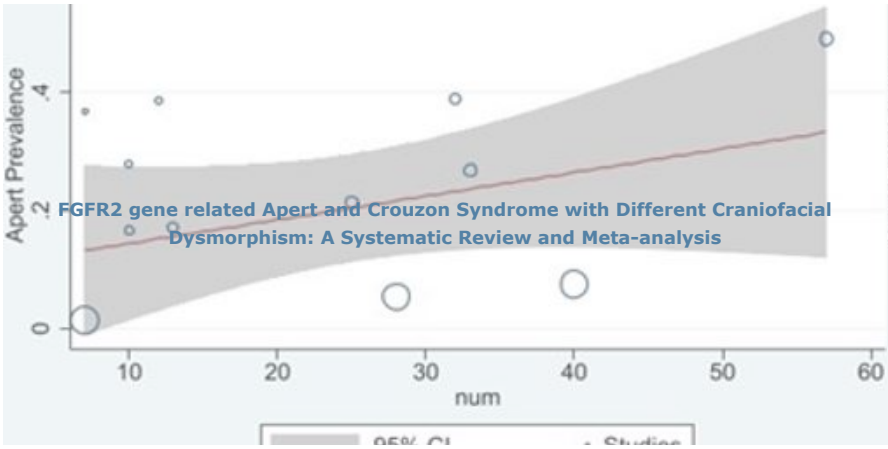

Abstract

Background: This study aims to compare Craniofacial dysmorphism like maxillary, mandibular, and dental arch dimensions, and cranial suture fusion prevalence in Apert and Crouzon Syndrome from the publicly available scientific information and also give insights to improve the findings of further studies. The protocol was submitted to the International Prospective Register of Systematic Reviews CRD42023395454 accessed 11 February 2023.

Material and Methods: On a large scale interval from January 2000 to January 2023 a comprehensive search on different database platforms: PubMed, Google Scholar, Cochrane, Web of Science, and Wiley online library. PRISMA (Preferred reporting item for Systematic Review and Meta-Analyses) guidelines were followed to conduct this systematic review. The meta-analysis was carried out by calculating the random effects model and pooled mean proportions with 95% confidence intervals (CI).

Results: A total of 53 studies were considered worthy, but 39 were excluded due to unusable data formats. The I2 index provides a better way of assessing effect size heterogeneity. Forest plots were generated to visualize the heterogeneity of the individual outcome. Subgroup analyses were performed for each outcome to assess the potential, differences in effect sizes. Effect size and heterogeneity of the dental arch are more in CS (I2: 58%, 95%CI 0.01,0.29, P=0.12) and least in AS (I2: 52%;95%CI 0.01;0,27, P=0.15). Effect size and heterogeneity of maxilla of AS patients (I2: 91%, 95%CI 0.09;0.47, P<0.01) and CS (I2: 94%,95%CI 0.07;0.64, P<0.01). We observed significant heterogeneity in AS and CS patients.

Conclusion: This review demonstrates the large variation in cephalometric measurements in CS and AS patients. The CS patient had a smaller skull and mandible volume than the AS patient. AS had an anterior crossbite (p<0.001) and CS had an edge-to-edge bite (p<0.011). CS tends to have short and flat cranial bases, smaller orbital volumes, and cleft palates.

Keywords: *: Apert, Cranium, Crouzon, Craniosynostosis, Dental Arches, FGFR2. Maxillary, Mandibular, Proptosis*

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5.36% Plagiarism. Authors state no conflict of interest. Non Funded. The conducted research is not related to either human or animals use. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Evidence in Context

What Know: The most commonFGFR2gene on chromosome 10 (10q25-10q26) was found pathogenic cause of AS and CS.
What New: Our systematic review provides updated information on the AS and CS craniofacial dysmorphism features.

To view

Introduction

The main manifestation present in Apert Syndrome (AS) and Crouzon Syndrome (CS) is craniosynostosis. Craniosynostosis is a condition of early fusion of the skull bones (Bhoj & Zackai, 2021; Lu et al., 2020). The early sutural fusion impairs skull growth and gives rise to craniofacial dysmorphism in the AS and CS (Das & Munshi, 2018; Lu et al., 2021). AS is one of the complex syndromes that causes craniosynostosis and hand and foot fusions. It was first described by Eugene Apert in 1842. It is also known as acrocephalosyndactyly (Junaid et al., 2023; Ko, 2016; Sawh-Martinez & Steinbacher, 2019). Other than craniosynostosis, craniofacial dysmorphism, visual impairments, cleft palate, and hearing loss are found in AS. The bilateral coronal synostosis is most frequently found in the AS (Alsaeed et al., 2023; Kumari et al., 2023; Massimi et al., 2019). Other metopic, lambdoid, and sagittal suture fusions are also found rarely in AS patients. There is a known genetic cause for the early closure of the cranial sutures in patients with AS (Choudhary et al., 2023; Faasse & Mathijssen, 2023; Koca, 2016; Tan & Mankad, 2018; Timberlake et al., 2023).

In 1912 Octave Crouzon first identified Crouzon syndrome (CS) (Al-Namnam et al., 2019; Balyen et al., 2017). This condition has complete penetrance and variable expressivity. CS is an autosomal dominant disorder, with common features such as the long face, proptosis prominent jaw, hypertelorism, exophthalmos, maxillary hypoplasia, hearing loss, and beaked nose, along with synostosis of coronal, sagittal, and lambdoid sutures (Motch Perrine et al., 2017; Rostamzad et al., 2022; Shlobin et al., 2022; Taylor & Bartlett, 2017; Tønne et al., 2020). The prevalence rate of AS has been estimated to be between 1/65,000 new-borns, and CS estimated as 1/25000 new-borns, without prediction by gender (Munarriz et al., 2020; Munib et al., 2023). AS and CS is associated with advanced paternal age, maternal infections, maternal drug consumption, and cranial inflammatory process (Fernandes et al., 2016; Kyprianou & Chatzigianni, 2018; Lu et al., 2019; Sakamoto et al., 2021). More than 98% of patients of AS and CS are caused by Fibroblast Growth Factor (FGFR2) gene-specific missense pathogenic mutations at chromosome 10q25-10q26 (Azoury et al., 2017; Morice et al., 2020). The FGFR belongs to the family of mitogenic signaling molecules that play an important role in the control of cell proliferation and survival (Luong et al., 2019; Ma et al., 2023).

AS and CS Patients fibroblasts are not able to produce the essential fibrous material in several craniofacial tissues, including bone sutures and cartilage, and during odontoblast formation and regeneration (Di Rocco et al., 2023; Elarjani et al., 2021; Hoshino et al., 2023). Most of the variations are missense variations in the*FGFR2*leading to craniofacial dysmorphism, and hand and feet malformations. Several syndromes are associated with*the FGFR2*gene. These phenotypes also include Antley Bixler syndrome, Beare Stevenson syndrome with cutis gyrata, Pfeiffer syndrome, Jackson Weiss syndrome, and Saethre Chotzen syndrome clinically classified as per additional digital anomalies, skin furrows and skeletal bowing and synostoses (Kiziltug et al., 2023; Pinto et al., 2023; Stanton et al., 2022).

In AS and CS patients the most commonly explored features are asymmetry in mandibular width, height and length, dental arch dimensions, and cranial suture fusion. In this review, we discuss the*FGFR2*gene-related craniofacial dysmorphism of rare syndromes which include AS and CS.This is the first systematic review focused on craniofacial dysmorphism of two syndromes associated with one*FGFR2*gene. This meta-analysis aims at better understanding the craniofacial dysmorphism in AS and CS by exploring the previously published scientific literature.

Material and Methods

This systematic review was carried out according to the preferred reporting methods for systematic reviews and meta-analysis (PRISMA 2020) guidelines [Table S1] (Page et al., 2021). The protocol was submitted to the International Prospective Register of Systematic Reviews CRD42023395454 accessed 11 February 2023.

Search Eligibility

Search includes peer-reviewed journals and publications that have full-text articles on AS and CS being discussed. Among the different types of research that have been ruled out are animal mice studies, clinical case reports, pilot studies, bibliographic reviews, book chapters, and systematic reviews. The four main steps included in selecting the article are Identification, Screening, Eligibility, and Inclusion.

There were case-control, cross-sectional, cohort studies that compared the Cephalometric CT scan, and radiographs of patients of AS, CS, and non-syndromic patients. Most studies discussed different aspects like maxillary, and mandibular dysmorphism, dental arch asymmetry, and cranial vault dysmorphism. All research papers that matched inclusion criteria were included. Researchers worked independently and reviewed title and abstract of all records to select all relevant studies and any discrepancies over results were resolved.

PICO Search strategy

The following numbers of electronic databases were used for search: PubMed, Cochrane, Medline, Web of Science from date of publication 2000 January to 2023 January [Table S3]. The main search terms used were craniofacial OR craniosynostosis (Apert syndrome) OR (craniofacial dysmorphism) AND (Crouzon syndrome) OR (craniofacial dysmorphism) AND (((Craniosynostosis [Title/Abstract])) OR (Cranium [Title/Abstract])) OR (FGFR2[Title/Abstract]).

Inclusion /exclusion criteria

The systematic review and meta-analysis inclusion criteria: studies on humans, papers written in English, children with descriptive studies such as case reports, case series, and randomized controlled trials, furthermore cohort studies, and case-control studies of Apert and Crouzon syndrome with craniofacial dysmorphism were included. This meta-analysis was not made on ethnicity or gender basis. Exclusion criteria: The cross-sectional studies, editorial, systematic reviews, and meta-analyses were excluded. The enrolled patients who had pathological fractures were excluded.

The search strategy algorithms for eligibility of studies and variables of interest were pre-specified in the protocol. The variables of interest were chosen and the subsequently anticipated heterogeneity in managing and reporting the same [Table S2].

Data Extraction

The researchers (SD, KD, MG) recaptured the information from different articles as authors with, year, country, and sample and used methodology in studies, independently screened retrieved studies for inclusion, based on titles and abstracts. The papers revealed craniofacial dysmorphism in AS, and CS based on clinical cephalometric CT scans and radiographs. The program Endnote X20 software was used for references.

Quality assessment

The Newcastle Ottawa Scale was used for qualitative evaluation of the studies included in the meta-analysis. The risk of bias was assessed based on three criteria selection, comparability, and outcome as mentioned in [Table S4]. The following domains were assessed: confirmed cases, representativeness of the cases, selections of control/comparator, definitions of control/ comparator, case, control/comparator, assessment of outcome, the same methodology used for cases for AS, CS, and NS, Nonresponse rate. Each of the domains was assessed with yes, no, or unclear. If the study met the criteria, points as (*) were given to that domain, and it was defined as a low risk of bias. If the study did not meet the criteria, or it was unclear, (-) points were given. The points for each item were added up, resulting in a total quality score. Studies with scores from 7-9, has high quality, 4-6, high risk, and 0-3 very high risk of bias. Newcastle –Ottawa Scale contains 9 items within 3 domains and the total maximum score is 9.

Statistical analysis

Descriptive statistics were used for the different craniofacial dysmorphisms in AS and CS. These meta-analysis proportions were carried out using the random effects model for the different anomalies, and pooled mean proportions with 95% CI's were calculated. A p-value of the small sample sizes and possibly extreme proportions was defined as statistically significant. Heterogeneity was evaluated by the I2 statistics. The software program is R version 4.1.2. for windows was used for the meta-analysis and forest plots (Balshem et al., 2011; Higgins & Thompson, 2002; Viechtbauer & Cheung, 2010; Wang, 2018).

Results

PECO population, exposure, comparator, and outcome criteria were used to find out the craniofacial dysmorphism in AS and CS. PECO criteria were used in the following ways people with AS and CS are referred to the research articles search and screening was performed according to the PRISMA 2020 chart.

Study selection

Our initial search strategy yielded 8685 papers from databases such as PubMed, Web of Science, Cochrane, and Science Direct. After the authors eliminated 6598 papers in the detection phase, the remaining 1198 papers were further screened (review, summary documents, non-human, editorials, case reports, commentaries, letters, and duplicate studies). A total of 53 studies were considered worthy, but 39 were excluded due to unusable data formats. Thus, based on the research objectives and inclusion and exclusion criteria, 14 studies were eventually included in this study and the full text of all included studies was retrieved [Fig:1].

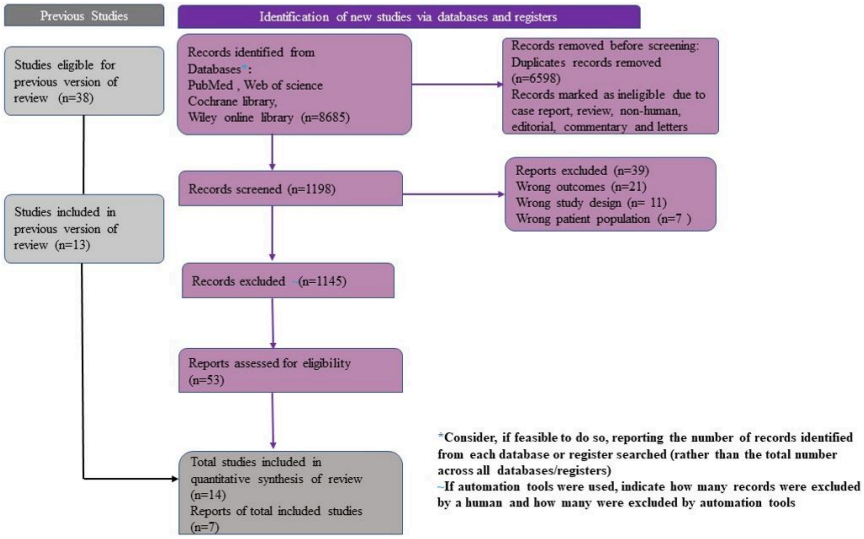

Figure 1: PRISMA (2020) chart detailing review approach and selection of studies.

Study Characteristics

All of the studies included were published in peer-reviewed journals. The main component of the included studies is summarised in [Table 1]. The studies used here were all published in high-quality academic publications. These research articles were cohort, observational, retrospective, and case-control study designs. In this meta-analysis, different studies were included from different places as three studies from the Netherlands, three from Brazil, each from France, the United States, Italy, Japan, and China. The most common gold standard method used in the studies was cephalometric radiographic measurement.

Fourteen studies were included, which mentioned both AS and CS patients. We included most of studies, which focused on comparing AS, CS, and non-syndromic/healthy controls based on craniosynostosis, dental and maxillary dimensions, and craniofacial manifestations. Craniosynostosis manifestations studies were from Sweden, Brazil, Italy, France, and Brazil. Kahnberg*et al.,*2010 (n=31) and Lu et al., 2020 (n=32) evaluated high cases of AS with craniosynostosis manifestation. Bouaound*et al.,*2020 evaluated the highest cases (n=25) of CS with craniosynostosis. Dental and maxillary manifestations studies were from the Netherlands, Japan, and China. The highest cases (n=40) of AS were studied by Reitsma*et al.,*2014 and CS (n=40) were studied by Reitsma*et al.,*2013. Craniofacial dysmorphism included studies from the United States America, the Netherlands, and Brazil. The highest cases of AS (n=18) and CS (n=16) were studied by Pinto*et al.,*2023.

Table 1: Characteristics of the studies on Apert and Crouzon syndrome included in this analysis [FFMBA: front-facial monobloc advancement; STL: Stereolithography; SNA: Sella, nasion, A point) indicates whether or not the maxilla is normal, prognathic, or retrognathic; SNB: Sella, nasion, B point) indicates whether or not the mandible is normal, prognathic, or retrognathic, PP palatal plane]

S.No.	Country	Study type	Apert Syndrome AS	Crouzon Syndrome CS	Non Syndromic NS	Age, years, mean(SD)/Median	Method used	Major findings in AS /CS
Craniosynostosis manifestation:								
Kahnberg et al., (2010)	Sweden	Retrospe-ctive study	31	12	19	7-8Y	Orthognathic surgical techniques	Patients who had sagittal split of the mandible, disturbances of sensitivity in a range of 10%–15% developed, as in all other orthognathic patients.
Lu et al., (2020)	Brazil	Case- Control	25	11	36	2D-16 Y	CT scan and Cephalometric measurements	This study attempts to clarify the individual influences of isolated bicoronal synostosis, Apert(AS) and Crouzon (CS) on skull base morphology.
Meazzini et al., (2020)	Italy	Case control	13	20	38	1-12 Y	CT Scan	The syndromic group showed a significant earlier ossification of all sutures compared to the nonsyndromic group
Bouaoud et al., (2020)	France	Retrospective Study	10	25	25	-	CT Scan analysis	The study aimed at assessing the variations in thickness of the supra-orbital bar in CS and AS before and after FFMBA using CT-scan data.
Lu et al., (2020)	Brazil	Prospective Observatinal	32	0	50	-	CT Scan analysis	Malformation of the middle cranial fossa is an early, perhaps the initial, pivotal cranial morphologic change in Apert syndrome.
Dental and maxillary manifestation:								
Reitsma et al., (2014)	Netherlands	Case -Control (Population based)	28	40	451	3.9-15.1 Y AS, others 2.9-17.9Y	Pnoramic radiographs analysis	Girls with AS had a statistically signifcant less mature dental maturity compared with controls
Reitsma et al., (2013)	Netherlands	Case- Control (Population based)	40	28	457	4-14 Y	CT scan with Cephalometric analysis	Maxillary intercanine width for patients with AS were increased, whilst other arch width variables showed no change
Kobayashi et al., (2020)	Japan	Cohort	7	12	0	Mean age, 12.3 ± 5.0 years),Mean age, 10.8 ± 2.9 years)	Orthopantomographic images and Cephalometric analysis	Cephalometric analysis revealed that AS patients had significantly more severe maxillary hypoplasia in two dimensions and increased clockwise mandibular rotation.
Lu et al., (2019)	China	Case-control	36	36	54	0-62y	CT scan and Cephalometric measurements	The narrowed angle between the mandible and the posterior cranial base in Apert skulls is consistent with the more limited nasopharyngeal and oropharyngeal airway space.
Craniofacial dysmorphism								
Lu et al., (2021)	USA	case –control	57	0	59	0.64-9.64 mean age	CT Scan	Apert syndrome, suggest that the associated cranial vault suture synostosis indeed does influence the development of the orbital bony structure.
Reitsma et al., (2013)	Netherlands	Case- Control (Population based)	7	6	486	8-19Y	CT Scan	The SNA, ANB, and SN/PP angles were signifcantly smaller in the syndromic patients, and the LFH ratio was signifcantly larger than control values.
Forte et al., (2014)	Brazil	Case-control	10	9	17	6-13Y	CT Scan	Midface retrusion in the Crouzon/Apert group is associated with altered sphenoid morphology (widened and retruded pterygoid plates), with a flatter and wider maxilla, suggesting diminished growth inferiorly and anteriorly
Pinto et al., (2023)	Brazil	retrospective longitudinal case-control study	18	16	34	AS mean age 14.4 years, CS was 13.4 years	Digitizing the sample models and obtaining the STL fles	Digital models were obtained from the archive of a public tertiary care hospital.

Meta-analysis

The analysis was carried out using the log risk ratio as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (i.e., τ2), was estimated using the restricted maximum-likelihood estimator. In addition to the estimate of τ2, the Q-test for heterogeneity and the I2 statistic are reported. In case any amount of heterogeneity is detected (i.e., τ^2>0^2>0, regardless of the results of the Q-test), a prediction interval for the true outcomes is also provided. Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the 100×(1−0.05/(2×k))100×(1−0.05/(2×k))th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided α=0.05 for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered to be influential. The analysis was carried out using R (version 4.2.2) and themeta forpackage (version 3.8.1) (Pollock et al., 2016). The measurements of craniofacial, and axial skeleton only were included in the analysis. For results interpretation of the meta-analysis, caution should be exercised. Due to the large variation in cephalometric measures, only a few were added to the meta-analysis forest plots.

This analysis found the difference between AS and CS patients. The CS patient had a smaller skull and mandible volume than the AS patient. In patients who had a sagittal split of the mandible, disturbances of sensitivity in a range of 10%–15% developed, as in all other orthognathic patients (Raposo-Amaral et al., 2014; Reitsma et al., 2014; Reitsma et al., 2013). The bicoronal synostosis in the cranium was majorly found in AS and CS on skull base morphology. Frontal bones were not thick in AS patients but found children significantly thicker frontal bones with CS. Cephalometric analysis revealed that AS patients had significantly more severe maxillary hypoplasia in two dimensions and increased clockwise mandibular rotation. The CS patients predicted no change in the maxillary intercanine width and intermolar width but, AS has increased maxillary intercanine width (Elmi et al., 2015; Kobayashi et al., 2021; Nur et al., 2014). With growth phase of children, maxillary and mandibular intercanine increased in CS whereas no change in mandibular and maxillary intercanine is predicted in AS (Forte et al., 2014; Khonsari et al., 2016).

The anterior maxillary region is more affected in AS patients whereas less affected in CS. AS had an anterior crossbite ($p<0.001$) and CS had an edge-to-edge bite ($p<o.o11$) (Pinto et al., 2023). CS tends to have shorter and flatter cranial bases, smaller orbital volumes, and cleft palates. Dental development of both AS and CS children was delayed as with normal ones (Spruijt et al., 2016). There was a statistically significant difference in maxillary and dental arches outcomes between patients with AS and CS. A total of seven studies were reported for outcomes. The I2 index provides a better way of assessing effect size heterogeneity. Forest plots were generated to visualize heterogeneity of individual outcome. Subgroup analyses were performed for each outcome to assess potential, differences in effect sizes. Effect size and heterogeneity of dental arch are more in CS (I2: 58%, 95%CI 0.01,0.29, P=0.12) and least in AS (I2: 52%;95%CI 0.01;0,27, P=0.15). Effect size and heterogeneity of maxilla of AS patients (I2: 91%, 95%CI 0.09;0.47, P<0.01) and CS (I2: 94%,95%CI 0.07;0.64, P<0.01). A significant heterogeneity in AS and CS patients was observed[Fig:2].

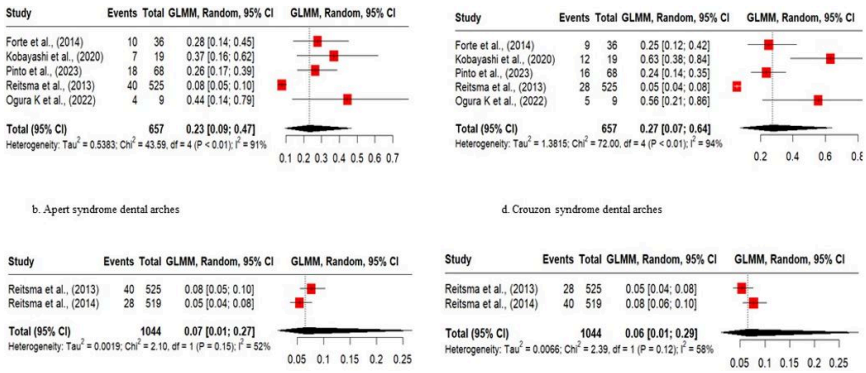

Figure 2: Forest plot based on the proportion of Apert and Crouzon syndrome. Forest plots were generated to visualize the heterogeneity of the individual outcome. Effect size and heterogeneity of the dental arch more in the least in AS. The CS patients predicted no change in the maxillary intercanine width and intermolar width but maxillary intercanine width for patients with AS increased.

Risk of bias

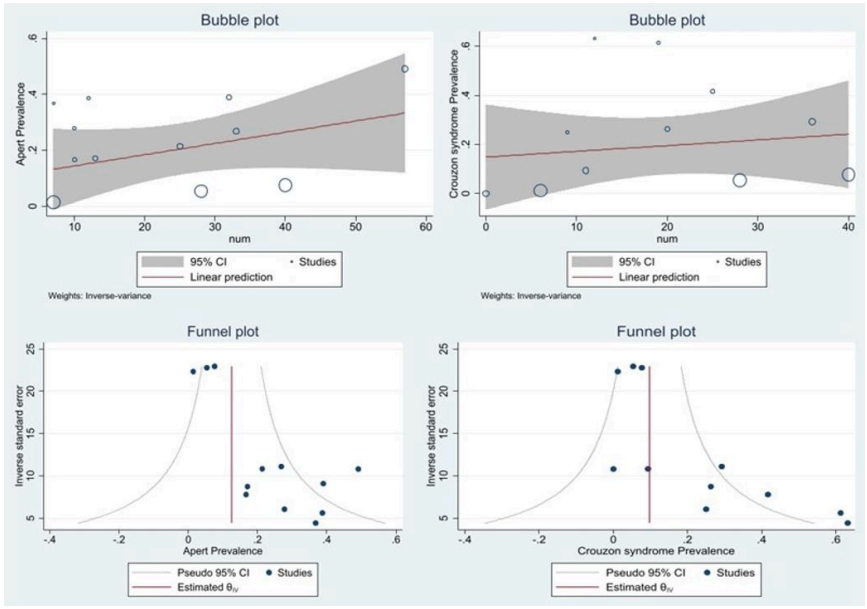

Figure 3: Bubble and Funnel plot based on the proportion of Apert and Crouzon syndrome. Asymmetry in the funnel plot indicates a lack of homogeneity and indicates biases.

A funnel and Bubble plot was generated to visualize the risk of bias among the studies. The Bubble Plot shows the relation between study-specific effect size where the size of each bubble is proportional to the precision of each study. AS and CS funnel plots showed no obvious risk of bias in Figure. Asymmetry in the funnel plot indicates a lack of homogeneity and indicates biases. The reason for asymmetry can be caused by different methodological designs and different sample sizes. Additional language bias, only English language is used and citation bias may also affect the asymmetry [Fig: 3].

Discussion

The current meta-analysis was performed to compare the craniofacial manifestations of AS, and CS patients. The most common*FGFR2*gene on chromosome 10 (10q25-10q26) was found pathogenic cause of AS and CS. Fibroblast growth factors are unable to produce the essential fibrous material in craniofacial tissues, such as bone sutures and cartilage, and odontoblast formation (Luong et al., 2019; Morice et al., 2020; Timberlake et al., 2023). This protein is one of the four*FGFRs*responsible for the formation of blood vessels, wound healing, embryonic evolution, and regulation of cellular division, growth, and maturation (Munib et al., 2023; Sawh-Martinez & Steinbacher, 2019; Shlobin et al., 2022). Gain of function due to*FGFR2*pathogenic variant causes has an impact on dental abnormalities, early fusion of sutures which function in the fusion process of skull bones, facial asymmetry, prominent forehead, abnormal eyelids closing, and limb bone fusion. Due to early closure of the sutures other health issues also acquired as intellectual development, increased intracranial pressures (Munarriz et al., 2020; Tønne et al., 2020). CS patients tend to have shorter skull bases, v-shaped maxillary arches, wider dental spacing, cleft palate and edge-to-edge bite, and minor limb malformations. This review demonstrates the large variation in cephalometric measurements in AS and CS patients. The maxillary intercanine width for patients with AS increased and CS patients predicted no change in the maxillary intercanine width and intermolar width. With the growth period of children, the maxillary and mandibular intercanine increased in CS whereas no change in mandibular and maxillary intercanine during the growth period was predicted in AS. The anterior maxillary region is more affected in AS patients whereas less affected in CS. AS had an anterior crossbite ($p<0.001$) and CS had an edge-to-edge bite ($p<0.011$) (Pinto et al., 2023).

The patients of AS were found with clinical features of limb malformations compared to CS patients. Increased mandibular asymmetry, increased lower facial height ratios, decreased transverse dimensions, an increased inclination of the palatal plane, and a more protruding mandible were observed in the AS patients. Reductions in maxillary and mandibular volume in CS patients but this is mostly age-related (Andersson et al., 2010; Khonsari et al., 2016; Kreiborg & Cohen Jr, 2010). The orbital sphere expansion is limited in CS patients as compared to AS. Only a few studies are found to be significant for this meta-analysis. As an outcome of this study, we found some minor differences in the patients of AS and CS.

More craniofacial measurements from different regions are needed to clarify the estimate of the maxilla's and mandible's vertical and anteroposterior positions for a definitive conclusion.In this meta-analysis, we conducted the literature search in the English language articles which was conducted in the period from January 2000 to 2023 January. Only the relevant information is taken from the previous literature. The literature research is taken which explains the measurements and comparison of AS, and CS with healthy control NS patients.

Conclusion

Our systematic review provides updated information on the AS and CS craniofacial dysmorphism features. The main focus is on the maxillary, dental arch dimension, and craniosynostosis. Due to limited literature on specific craniofacial features, we could include some studies focusing on selected craniofacial dysmorphism which covers both syndromes. In these two craniosynostosis syndromes, the phenotypes match to the patients of similar phenotypes rather than to the patient's parent's phenotypes. In AS patient's midface protrusion, mandible down (retrognathia), smaller orbital volume, hypoplasia, delay in dental development, open bites, cleft palate, brachycephaly as craniosynostosis. Additionally, severe limb malformations were noted. CS patients tend to have shorter skull bases, v-shaped maxillary arches, wider dental spacing, cleft palates and edge-to-edge bites, and minor limb malformations. This review demonstrates the large variation in cephalometric measurements in AS and CS patients. The maxillary intercanine width for patients with AS increased and CS patients predicted no change in the maxillary intercanine width and intermolar width. With the growth period of children, the maxillary and mandibular intercanine increased in CS whereas no change in mandibular and maxillary intercanine during the growth period was predicted in AS. The anterior maxillary region is more affected in AS patients whereas less affected in CS. AS had an anterior crossbite ($p<0.001$) and CS had an edge-to-edge bite ($p<0.011$). In the case of craniosynostosis, AS patients' influences of isolated bi-coronal synostosis, and CS tend to have short and flat cranial bases and smaller orbital volumes of craniofacial morphology. Malformation of the middle cranial fossa is an early, perhaps the initial, cranial morphologic change in AS patients. The CS patient had a smaller skull and mandible volume compared to the AS patients. CT scans do help patients pursue orthodontic and maxillofacial treatment alone or choose assisted surgery for their respective expansion.

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