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ORAL CONDITIONS AND DENTAL PHENOTYPES IN SUBJECTS WITH PIERRE ROBIN SYNDROMIC SEQUENCE: LITERATURE REVIEW

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ABSTRACT **Purpose:** The purpose of this study was to conduct a critical literature review on oral conditions and dental phenotypes described in patients with Syndromic Pierre Robin Sequence (SPRS). **Materials and Methods:** The review of the literature on oral conditions and dental phenotypes was performed in patients with SPRS through an active search in three databases, PubMed, Medline and SciELO, using the descriptors: "Dental Abnormalities", "Tooth Abnormalities", "Oral Diagnosis", "Dentistry", "Oral Health", combined with: "Pierre Robin Syndrome", "Mandibulofacial Dysostosis", "22q11 Deletion Syndrome", and "Stickler". For the selection of manuscripts, papers published between 2014 and 2022 were analyzed according to the inclusion criteria. **Results:** Were selected 7 studies addressing dental conditions or dental anomalies in SPRS in the 3 syndromes chosen: 22q11.2 Deletion Syndrome (22q11.2 DS), Treacher Collins Syndrome (TCS) and Stickler Syndrome (SS). In the 3 studies on 22q.11 DS, it was observed that the most reported anomalies were dental agenesis, impacted canine, enamel hypoplasia and supernumerary tooth, respectively. In studies on TCS, with a reduced number of subjects, dental crowding and occlusal changes were the most common oral conditions. No study addressed the dental phenotypes of SS. **Conclusions:** The importance of further studies on this specific topic is emphasized, since SPRS involves micrognathia and mandibular retroposition. Thus, these clinical findings can be valuable for all professionals who provide assistance to these patients. Thus, based on this knowledge, it is possible to plan more effective rehabilitation, contributing to improving the quality of life of these individuals.

KEYWORDS : Dental Anomalies, Pierre Robin Sequence, 22q11.2 Deletion Syndrome, Treacher Collins Syndrome

INTRODUCTION

The Pierre Robin Sequence (PRS) is a rare congenital anomaly described by Pierre Robin.[32] It is characterized by the triad of micrognathia, glossoptosis and airway obstruction, with the cleft palate as an aggravating factor since it was present in 90% of the cases.[21,31] Prevalence estimates vary from one per 8,500 to 20,000 live births[4,5,29] and without distinction between the sex, except for chromosome X-linked inheritance.[17] The etiology of this condition is still unknown and there are three proposed theories to explain its pathogenesis: the mechanical theory, which is the most widely accepted and proposes mandibular hypoplasia as the initial event;[2] the neurological maturation theory; and the mandibular compression theory.[13] In addition, several authors have investigated a possible genetic determination in the etiology of the PRS, but it still remains uncertain.[6,18,34]

Although the PRS may occur isolated, some associations with other malformations have been described.[27] Thus, Cohen (1976) classified the PRS in three groups due to the wide phenotype variability and the different genetic contributions for each one: Isolated Pierre Robin Sequence (IPRS) for cases without associations to other malformations or syndromes; Syndromic Pierre Robin Sequence (SPRS), which happens as part of a specific syndrome; and Anomaly-associated Pierre Robin Sequence (APRS), when it occurs simultaneously to one or more anomalies that do not stablish a specific syndrome.[8] Approximately 26% to 83% of the diagnoses of PRS are part of a syndrome.[14,17] Until today, more than 40 associated syndromes were described, being the most common the Stickler Syndrome (SS), Treacher Collins Syndrome (TCS) and 22q11.2 Deletion Syndrome (22q11.2 DS).[12,16,19]

Stickler syndrome is connective tissue disorder that is a clinically based diagnosis involving myopia, cataract, retinal detachment, hearing loss, midface underdevelopment, joint abnormalities, and cleft palate.[33] TCS is a deformation of facial structures produces a characteristic appearance that includes malar hypoplasia, periorbital soft tissue anomalies, maxillomandibular hypoplasia, and ear anomalies. Both are genetic disorders caused by COL2A1 and TCOF1 genes, respectively.[28,33] Already, the 22q11.2 DS is diagnosed in patients with a submicroscopic deletion of chromosome 22 and has various clinical features including congenital heart problems, specific facial features, frequent infections, developmental delay, learning problems and cleft palate. All the syndromes may be associated or not with PRS.[24]

Even though the PRS manifests the characteristic phenotypes in the oral cavity, there are few studies investigating the dental manifestations.[9,20,23] A study conducted by Castillo (2019) with subjects with IPRS observed that 92.72% presented at least one dental anomaly, the most common of which were, respectively, taurodontism, dental agenesis and dilacerated roots. No cases of supernumerary teeth, microdontia or macrodontia were observed.[22] These findings show that in addition to the complexity of medical treatment, is also expected a complex dental treatment in IPRS patients due to the high incidence of dental anomalies. However, no study has evaluated dental anomalies in SPRS so far. Thus, this study aims at performing a critical review of the literature regarding the dental anomalies described in the main SPRS.

MATERIALS AND METHODS

This critical review chose as research strategy an active search for information in three electronic databases [PubMed (https://pubmed.ncbi.nlm.nih.gov),Medline(http://bases. bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=MEDLINE&lang=p&form=B) and SciELO (Scientific Electronic Library Online; https://scielo.org] using the intersection of the following health sciences descriptions (DesC/MeSH, created by BIREME to serve in indexing papers from scientific journals; https://decs.bvsalud.org): "Dental Abnormalities", "Tooth Abnormalities", "Dental Anomalies", "Oral Diagnosis", "Dentistry", "Oral Health", "Pierre Robin Syndrome", "Mandibulofacial Dysostosis", "22q11.2 Deletion Syndrome", and "Stickler Syndrome". For the selection of manuscripts, papers published between 2014 and 2022 were analyzed according to the inclusion criteria. This process resulted in a total of 261 papers, excluding the duplicates.

The papers were submitted to a careful selection process, in order to identify the dental anomalies in the cases of SPRS. Firstly, titles and abstract were examined and considered according to the following inclusion criteria: only case reports and clinical research with SS, TCS and 22q11.2 DS with PRS. After that, the papers were read in full and only studies that could identify clinically and/or radiographically the dental anomalies were included. All studies who had no oral clinical or radiographic images of the cases of SS, TCS and 22q11.2 DS with PRS were excluded from this study. Of the 261 papers, 254 were excluded (240 not addressed PRS and/or dental anomalies in cases of SS, TCS and 22q11.2 DS; nine not addressed the syndromic form with PRS; and five were literature review or letters to editor) and seven papers were selected for this literature review (one was clinical research and six case reports) (Figure 1).

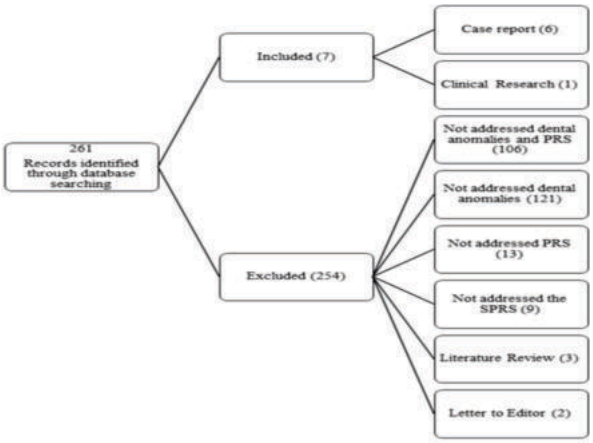

Figure 1. Flowchart showing the inclusion and exclusion criteria of studies

RESULTS

Of the seven papers included in this study, two were about the TCS and five with 22q11.2 DS. No study was found regarding the Stickler Syndrome (SS). To all the studies, the methods employed for the evaluation were medical records, clinical examinations, intrabuccal and extrabuccal photographs, panoramic and cephalometric radiographs, dental models, and a 3D image of the face.

In the table 1 shows two studies with TCS. In the first showed one patient with impacted lower canines and crowded teeth, and in the second, one patient presenting crowded teeth.

Table 1. Dental anomalies in the patients with Treacher Collins Syndrome included in this review.

Treacher Collins Syndrome					
Author	Year	Country	Type of Study	Number of Subjects	Dental anomalies
Renju et al.30	2014	India	Case Report	1	Crowded teeth
Chung et al.7	2014	USA	Case Report	1	Impacted lower canine (N=2)
					Crowded teeth

In relation the 22q11.2DS, one clinical research and four case report was found. In the clinical research four of the 20 patients had dental agenesis, three patients presented impacted upper canines, two upper lateral incisors hypoplasia, one supernumerary tooth, and one dental transposition. Furthermore, the clinical cases report showed three patients with dental dysmorphic feature, macrodontia and crowding of the teeth, one with ectopic eruption, one with supernumerary tooth, and one with delayed eruption (Table 2).

Table 2. Dental Anomalies In The Patients With 22q.11.2 Deletion Syndrome Included In This Review.

22q11.2 Deletion Syndrome					
Author	Year	Country	Type of Study	Number of Subjects	Dental anomalies
Vaz et al.36	2015	Portugal	Case Report	2	Supernumerary (N=1)
Matthews-Brzozowska et al.23	2015	Polônia	Case Report	1	Delayed eruption (N=1)
Lewyllie et al.20	2017	Belgium Western Europe	Clinical Research	20	Dental agenesis (N=4)
					Impacted upper canine (N=3)
					Enamel
					Supernumerary
					Transposition
AlQarni et al.3	2018	Saudi Arabia	Case Report	1	Ectopic eruption (N=2)
Yamada et al.37	2019	Japan	Case Report	3	Enamel hypoplasia
					Macrodontia
					Crowded teeth

DISCUSSION

In this study we evaluated the dental anomalies in patients with SPRS, including 22q11.2 Deletion Syndrome, Stickler Syndrome, and the Treacher Collins Syndrome in the three selected databases. Even with wide search parameters, we obtained a total of seven studies, being five about the 22q11.2DS and two TCS. It is noteworthy that no study was found from 2014 to 2020 regarding dental anomalies in subjects with SS, even though it is the most common syndromic form in the Pierre Robin Sequence.[19] Corroborating with these results, studies show only orthodontic changes as retroclined incisors, a large overjet and overbite due to micrognatia present in SS.[1,35]

Of the seven studies included in this study, one clinical research[20] analyzed 20 patients and six case report[7,23,30,36,3,37] included nine patients. A total of 29 patients with SPRS were analyzed, being 27 with 22q11.2DS and two with TCS. The results show that dental anomalies of position, number and structure were the most common in the SPRS. From this sample, dental agenesis, supernumeraries, impacted canines, crowded teeth, dental transposition, ectopic eruption, delayed eruption, enamel hypoplasia and macrodontia were reported in subjects with 22q11.2DS. In subjects with TCS were crowded teeth and impacted teeth.

Although, the literature on dental anomalies in 22q11.2DS and TCS is rather sparse, our review revealed that dental anomalies are common. In 22q11.2DS was reported a high prevalence of dental agenesis (four of 20 patients), as also found in older studies.[15,25,26] These studies showed dental agenesis mainly in primary affected teeth being mandibular incisors, maxillary lateral incisors and maxillary second premolars.[15,20,25,26] In addition, studies reported cases of 22q11.2DS with complete dental formation.[3,10] A solitary median maxillary central incisor was reported in a case of 22q11.2DS,[38] supernumerary,[20,36] macrodontia,[37] and delayed tooth formation and eruption were also reported.[38]

Structural defects of tooth enamel in the quality and quantity of enamel are also common findings, with a predominance of hypomineralization, especially in permanent teeth.[3,25] However, in syndromic patients, the increased prevalence of caries and gingivitis still remains related to poor oral hygiene. Thus, health providers and family members should be motivated by and informed about these oral health challenges, and access to dental care should be ensured. Routine dental visits will also help maintain and improve the oral health of patients.

Few dental anomalies repeated in more than one case and no patient presented all characteristics simultaneously. Thus, analyzing the data found in the studies, we may infer that the dental anomalies observed in subjects with 22q11.2DS are similar to those observed in subjects with non-syndromic cleft palate, with a high prevalence of dental agenesis, followed by impacted canines and dental hypoplasia.[11] Some authors attribute this higher prevalence of agenesis to the presence of cleft palate as part of the typical phenotype. As such, the shortening of the dental arch due to the presence of the cleft palate and the characteristics of the 22q11.2DS could be responsible by the impacted canines and crowed teeth.

Furthermore, the studies included in this review analyzing subjects with TCS observed many oral conditions, in particular orthodontic alterations, with a predominance of crowded teeth, which was present in two case reports. This characteristic in subjects with TCS may be explained by the reduced maxillomandibular dimensions characteristic of the syndrome, which is also called mandibulofacial dysostosis. Therefore, in this syndrome, there is often a difference

between the size of the teeth and the dimensions of the arches, leading to alterations in dental positioning and occlusion.[28,33]

CONCLUSIONS

Although the syndromes associated to PRS (SPRS) are rare and few studies were published showing the dental features, this review supports that dental anomalies of position, number and structure are common clinical findings in the SPRS. Dental agenesis, supernumeraries, impacted canines, crowded teeth, dental transposition, ectopic eruption, delayed eruption, enamel hypoplasia and macrodontia in the 22q11.2DS, and crowded teeth and impacted teeth in the TCS. These clinical findings may be valuable to all professionals that provide care to these patients. In addition, by improving their knowledge regarding the dental condition of these subjects and their respective dental anomalies, the dentists may be able to plan more effective rehabilitation treatments and improve the quality of life of these subjects.

Conflicts of interest: none

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REFERENCES

1. Acke F. R., Dhooge I. J., Malfait F., De Leenheer E. M. R., & De Pauw G. A. M. (2016). Cephalometrics in Stickler Syndrome: objectification of the typical facial appearance. Journal Of Cranio-Maxillo-Facial Surgery, 44 (7), 848-853. doi:10.1016/j.jcms. 2016.04.010.
2. Aggarwal S., & Kumar A. (2003). Fetal hydrocolpos leading to Pierre Robin Sequence: an unreported effect of oligohydramnios sequence. Journal Of Perinatology, 23(1), 76-78. doi: 10.1038/sj.jp.7210846.
3. AlQarni M., Alharbi A., & Merdad L. (2018). Dental management of a patient with 22q11.2 Deletion Syndrome (22q11.2DS). BMJ Case Reports, 2018, bcr2018225765. doi: 10.1136/bcr-2018-225765.
4. Breugem C. C., & Mink Van Der Molen A. B. (2009). What is "Pierre Robin Sequence"? Journal Of Plastic, Reconstructive & Aesthetic Surgery, 62(12), 1555-1558. doi: 10.1016/j.bjps.2008.06.050.
5. Bush P. G., & Williams A. J. (1983). Incidence of the Robin Anomalad (Pierre Robin Syndrome). British Journal Of Plastic Surgery, 36(4), 434–437. doi: 10.1016/0007-1226(83)90123-6.
6. Carroll D. B., Peterson R. A., Worton E. W., & Birnbaum L. M. (1971). Hereditary factor in the Pierre Robin Syndrome. British Journal Of Plastic Surgery, 24(1), 43-47. doi: 10.1016/s0007-1226(71)80008-5.
7. Chung J. Y., Cangialosi T. J., & Eisig S. B. (2014). Treacher Collins Syndrome: a case study. American Journal Of Orthodontics And Dentofacial Orthopedics, 146(5), 665-672. doi: 10.1016/j.ajodo.2014.06.019.
8. Cohen Jr M. M. (1976). The Robin Anomalad: its nonspecificity and associated syndromes. Journal Of Oral Surgery, 34(7), 587-593. Recovered from https://pubmed.ncbi.nlm.nih.gov/1064704/.
9. Dalben G. S., Costa B., & Gomide M. R. (2006). Prevalence of dental anomalies, ectopic eruption and associated oral malformations in subjects with Treacher Collins Syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, And Endodontics, 101(5), 588-592. doi: 10.1016/j.tripleo.2005.07.016.
10. Dalben G. S., Richieri-Costa A., & Taveira L. A. A. (2008). Tooth abnormalities and soft tissue changes in patients with Velocardiofacial Syndrome. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, And Endodontics, 106(2), e46-e51. doi: 10.1016/j.tripleo.2008.04.019.
11. Dixon D. A. (1968). Defects of structure and formation of the teeth in persons with cleft palate and the effect of reparative surgery on the dental tissues. Oral Surgery, Oral Medicine, And Oral Pathology, 25(3), 435-446. doi: 10.1016/0030-4220(68)90019-4.
12. Evans A. K., Rahbar R., Rogers G. F., Mulliken J. B., & Volk M. S. (2006). Robin Sequence: a retrospective review of 115 patients. International Journal Of Pediatric Otorhinolaryngology, 70(6), 973-980. doi: 10.1016/j.ijporl.2005.10.016.
13. Giudice A., Barone S., Belhous K., Morice A., Soupre V., Bennardo F., … Picard A. (2018). Pierre Robin Sequence: A comprehensive narrative review of the literature over time. Journal Of Stomatology, Oral And Maxillofacial Surgery, 119(5), 419-428. doi: 10.1016/j.jormas.2018.05.002.
14. Gomez-Ospina N., & Bernstein J. A. (2016). Clinical, cytogenetic, and molecular outcomes in a series of 66 patients with Pierre Robin Sequence and literature review: 22q11.2 Deletion Is Less Common Than Other Chromosomal Anomalies. American Journal Of Medical Genetics. Part A, 170A(4), 870–880. doi: 10.1002/ajmg.a.37538.
15. Heliövaara A., Rantanen I., & Arte S. (2011). Dental development and tooth agenesis in children with Velocardiofacial Syndrome. International Journal Of Paediatric Dentistry, 21(6), 446-450. doi: 10.1111/j.1365-263X.2011.01148.x.
16. Hsieh S. T., & Woo A. S. (2019). Pierre Robin Sequence. Clinics In Plastic Surgery, 46(2), 249-259. doi: 10.1016/j.cps.2018.11.010.
17. Jakobsen L. P., Ullmann R., Christensen S. B., Jensen K. E., Mølsted K., Henriksen K. F., … Tümer Z. (2007). Pierre Robin Sequence may be caused by dysregulation of SOX9 and KCNJ2. Journal Of Medical Genetics, 44(6), 381-386. doi: 10.1136/ jmg. 2006.046177.
18. Jakobsen L. P., Knudsen M. A., Lespinasse J., Ayuso C. G., Ramos C., Fryns J.-P., … Tommerup N. (2006). The genetic basis of the Pierre Robin Sequence. The Cleft Palate-Craniofacial Journal, 43(2), 155-159. doi: 10.1597/05-008.1.
19. Karempelis P., Hagen M., Morrell N., & Roby B. B. (2020). Associated syndromes in patients with Pierre Robin Sequence. International Journal Of Pediatric Otorhinolaryngology, 131, 109842. doi: 10.1016/j.ijporl.2019.109842.
20. Lewyllie A., Roosenboom J., Indencleef K., Claes P., Swillen A., Devriendt K., … Verdonck A. (2017). A comprehensive craniofacial study of 22q11.2 Deletion Syndrome. Journal Of Dental Research, 96(12), 1386-1391.doi:10.1177/ 0022034517720630.
21. Marques I. L., Sousa T. V., Carneiro A. F., Peres S. P. B. A., Barbieri M. A., & Bettiol H. (2005). Sequência de Robin – Protocolo único de tratamento. Jornal de Pediatria, 81(1), 14-22. doi: 10.1590/s0021-75572005000100005.
22. Mateo-Castillo J. F., Pagin O., Carvalho I. M. M., Olano-Dextre T. L., & Neves L. T. (2019). Novel dental phenotype in Non-Syndromic Pierre Robin Sequence: a retrospective study. Archives Of Oral Biology, 97,170-175. doi:10.1016/ j. archoralbio. 2018.10.031.
23. Matthews-Brzozowska T., Baranowska J., Rogiński P., Obersztyn E., & Cudziło D. (2015). Malocclusions and craniofacial anomalies in a child with Velo-Cardio-Facial Syndrome. Developmental Period Medicine, 19(4), 490-495. Recovered from https://europepmc.org/article/med/26982759.
24. McDonald-McGinn D. M., Hain H. S., Emanuel B. S., & Zackai E. H. 22q11.2 Deletion Syndrome. (1999, September 23). In: Adam M. P., Ardinger H. H., Pagon R. A., Wallace S. E., Bean L. J. H., Gripp K. W., & Amemiya A., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, 1993-2020. Available from:https://www.ncbi.nlm.nih.gov/books/NBK1523/.
25. Nordgarden H., Lima K., Skogedal N., Følling I., Storhaug K., & Abrahamsen T. G. (2012). Dental developmental disturbances in 50 individuals with the 22q11.2 Deletion Syndrome; Relation To Medical Conditions? Acta Odontologica Scandinavica, 70(3), 194-201. doi: 10.3109/00016357.2011.629624.
26. Oberoi S., Huynh L., & Vargervik K. (2011). Velopharyngeal, speech and dental characteristics as diagnostic aids in 22q11.2 Deletion Syndrome. Journal Of The California Dental Association, 39(5), 327-332. Recovered from https://pubmed.ncbi.nlm.nih.gov/21721477/.
27. Pasyayan H. M., & Lewis M. B. (1984). Clinical experience with the Robin Sequence. The Cleft Palate Journal, 21(4), 270-276. Recovered from https://pubmed.ncbi.nlm.nih.gov/6595082/.
28. Plomp R. G., van Lieshout M. J. S., Joosten K. F. M., Wolvius E. B., van der Schroeff M. P., Versnel S. L., … Mathijssen I. M. J. (2016). Treacher Collins Syndrome: a systematic review of evidence-based treatment and recommendations. Plastic And Reconstructive Surgery, 137(1), 191-204. doi: 10.1097/PRS.0000000000001896.
29. Printzlau A., & Andersen M. (2004). Pierre Robin Sequence in Denmark: a retrospective population-based epidemiological study. The Cleft Palate-Craniofacial Journal, 41(1), 47–52. doi: 10.1597/02-055.
30. Renju R., Varma B. R., Kumar S. J., & Kumaran P. (2014). Mandibulofacial Dysostosis (Treacher Collins Syndrome): a case report and review of literature. Contemporary Clinical Dentistry, 5(4), 532-534. doi: 10.4103/0976-237X.142826.
31. Robin P. (1934). Glossoptosis due to atresia and hypotrophy of the mandible. American Journal Of Diseases Of Children, 48(3), 541-547.doi:10.1001/archpedi. 1934.01960160063005.
32. Robin P. (1923). La chute de la base de la langue considérée comme une nouvelle cause de géne dans la respiration naso-pharyngienne. Bulletin De l'Académie Nationale De Médecine, 89, 37-41.
33. Robin N. H., Moran R. T., & Ala-Kokko L.Stickler Syndrome. (2000, June 9) [updated 2017 Mar 16]. In: Adam M. P., Ardinger H. H., Pagon R. A., Wallace S. E., Bean L. J. H., Gripp K. W., … Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, 1993-2020. PMID: 20301479. Available from: https://pubmed.ncbi.nlm.nih.gov/20301479/.
34. Selvi R., & Priyanka A. M. (2013). Role of SOX9 in the etiology of Pierre – Robin Syndrome. Iranian Journal Of Basic Medical Sciences, 16(5), 700-704. Recovered from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3700045/.
35. Suda N., Handa S., Higashihori N, Ogawa T., Tsuji M., & Ohyama K. (2007). Orthodontic treatment of a patient with Stickler Syndrome. The Angle Orthodontist, 77(5), 931-939. doi: 10.2319/082406-347.
36. Vaz S.O., Pires R., Pires L. M., Carreira I. M., Anjos R., Maciel P., & Mota-Vieira L. (2015). A unique phenotype in a patient with a rare Triplication of the 22q11.2 region and new clinical insights of the 22q11.2 Microduplication Syndrome: a report of two cases. BMC Pediatrics, 15, 95. doi: 10.1186/s12887-015-0417-5.
37. Yamada M., Uehara T., Suzuki H., Takenouchi T., Yoshihashi H., Suzumura H., … Kosaki K. (2019). SATB2-associated syndrome in patients from Japan: linguistic profiles. American Journal Of Medical Genetics. Part A, 179(6), 896-899.doi: 10.1002/ ajmg.a.61114.
38. Yang H.-C., Shyur S.-D., Huang L.-H., Chang Y.-C., Wen D.-C., Liang P.-H., & Lin M.-T. (2005). Digeorge Syndrome associated with solitary median maxillary central incisor. Asian Pacific Journal Of Allergy And Immunology, 23(2-3), 159-163. Recovered from http://apjai-journal.org/wp-content/uploads/2018/01/13DiGeorge Syndrome Associated Vol23No2-3June-Sep2005P159.pdf.