Received: 21th November 2014 Accepted: 21st February 2015 Conflicts of Interest: None

Source of Support: Nil

Review Article

Oral and Craniofacial Clinical Signs Associated to Genetic Conditions in Human Identification Part I: A Review

Fouad Ayoub[1], Nicole Aoun[2], Hassan el Husseini[3], Houssam Jassar[4], Fida Sayah[5], Ziad Salameh[6]

Contributors:

[1]Dean and Professor, Department of Basic Sciences, School of Dentistry, Lebanese University, Beirut, Lebanon; [2]Instructor, Department of Oral Pathology and Diagnosis, School of Dentistry, Lebanese University, Beirut, Lebanon; [3]Instructor, Department of Endodontics, School of Dentistry, Lebanese University, Beirut, Lebanon; [4]Instructor, Department of Oral Surgery, School of Dentistry, Lebanese University, Beirut, Lebanon; [5]Instructor, Department of Preventive Dentistry, School of Dentistry, Lebanese University, Beirut, Lebanon; [6]Professor, Department of Research and Prosthodontics, School of Dentistry, Lebanese University, Beirut, Lebanon.

Correspondence:

Dr. Salameh Z. Department of Research and Prosthodontics, School of Dentistry, Lebanese University, Beirut, Lebanon. Phone: +961-71-247147, Fax: +961-1-582288. Email: drzsalameh@gmail.com

How to cite the article:

Ayoub F, Aoun N, Housseini H, Jassar H, Sayah F, Salameh Z. Oral and cranio-facial clinical signs associated to genetic conditions in human identification Part I: A review. J Int Oral Health 2015;7(5):81-86.

Abstract:

Background: Forensic dentistry is one of the most reliable methods used in human identification when other technique as fingerprint, DNA, visual identification cannot be used. Genetic disorders have several manifestations that can target the intra-oral cavity, the cranio-facial area or any location in the human body.

Materials and Methods: A literature search of the scientific database (Medline and Science Direct) for the years 1990 to 2014 was carried out to find out all the available papers that indicate oral, cranio-facial signs, genetic and human identification.

Results: A table with 10 genetic conditions was described with oral and cranio-facial signs that can help forensic specialist in human identification.

Conclusion: This review showed a correlation between genetics, facial and intra-oral signs that would help forensic ondontologist in the identification procedures.

Key Words: Craniofacial, forensic dentistry, genetic, human identification signs

Introduction

Forensic odontology involves the management, examination, evaluation, and presentation of dental evidence in criminal or civil proceeding.[1]

Forensic dentistry is mainly involved in the identification of deceased individuals.[2] Recognition of unknown bodies is associated to their facial appearance, when severe damage occurred to the face; palm and fingerprints are used for identification.[3,4] When physical identification and fingerprints cannot be used, dental identification remains one of the most reliable and frequently applied methods of identification, predominantly by comparisons of ante-mortem and post-mortem records.[5]

The most common methods of identification include visual identification, fingerprinting, serologic and DNA comparison, and anthropologic examination of bone. Each method has its advantages and disadvantages. They all rely on the principle that identification is derived from a positive correlation between known information about a person and findings from a physical examination of the decedent.[2]

In the last few years, technology has provided new instruments for the three-dimensional analysis of human facial morphology. Currently, quantitative assessments of dimensions, spatial positions, and relative proportions of distinctive facial features can be obtained for both soft- and hard- (skeletal and dental) tissues. Several methods of denture labeling were reported in order to identify edentulous persons.[6-8]

Genetics is a very important reference that is used in accurate identification of persons; genetic disorders have several manifestations that can target the intra-oral cavity, the craniofacial area, or any location in the human body[9,10].

The aim of this paper was to evaluate the association of the oral and craniofacial clinical signs observed in human identification procedure with specific genetic condition.

Materials and Methods

A search of the scientific database (Medline and Science Direct) for the years 1990 to 2014 was performed. Abstract, case report, clinical research, and review articles were included. Keywords used were genetic, forensic, identification, oral, craniofacial, manifestations, and dentistry.

Due to the very broad disorders/clinical signs associated with genetic conditions, a focus on the most frequent reported condition was selected (Table 1).

Oral-facial-digital syndrome

Oro-facial-digital syndrome type I (OFD I) or orofaciodigital dysostosis. The gene responsible for the syndrome is found

Table 1: Different intraoral and facial signs associated with genetic conditions.

Condition	Gene involved	Intra-oral signs	Extra-oral signs
Oral-facial-digital syndrome Type I	*CXORF5* (OFD I)	High arched palate Oligodontia Supernumerary teeth Micrognathia	Frontal bossing Facial asymmetry Ocular hypertelorism Cleft lip/palate Strabismus
Trisomy 13 or Patau syndrome	Chromosome 13 (15q deletion)	Dental caries Enamel hypoplasia Malocclusion Heavy calculus Decreased salivation Gingivitis	Microphthalmia Strabismus Iris coloboma Cleft lip/palate Depressed nasal bridge Stubby nose
Trisomy 21 or Down syndrome	Chromosome 21	Hypodontia Periodontal disease Missing teeth Taurodontism Malocclusion	Brachycephaly/flat occiput Upward slanting palpebral fissures/epicanthal folds
Turner syndrome	45X karyotype	Distal molar occlusion Narrow upper arch Wide lower arch Lateral crossbite Teeth are smaller than normal	Decreased maxillary growth Midface hypoplasia Wide micrognathic mandible
Klinefelter syndrome	Extra X or Y chromosome to 47, XXY	Dysmorphic Hypodontia Prognathism Short filtrum	Hypoplastic teeth Tooth crown larger Shovel shaped lateral incisors
Marfan syndrome	FBN1 gene	Stretch marks as pink, white or red streaks in the skin	Crowded teeth Small lower jaw High arched palate Dental caries and periodontal diseases
Axenfeld-Rieger syndrome	Mutations in PITX2 on ch 4q25, FOXC1 on 6p25, PAX6 on 11p13, and FOXO1A on 13q14	Glaucoma Craniofacial anomalies	Dental hypoplasia
Pycnodysostosis (the Toulouse-Lautrec syndrome)	Cathepsin K gene	Craniofacial anomalies Short head	Crowded teeth Periodontal disease
Apert syndrome	Mutation Of FGFR2	Flat occiput Short, broad nose with bulbous tip Brachycephaly Midface hypoplasia Hypotonic lips	Arched palate with bilateral swellings of the palatine processes Ectopic eruption and malocclusion Severe crowding Delayed eruption Thick gingiva Genetically missing teeth Anterior open bite Bilateral posterior cross-bite
Crouzon syndrome	Chromosome 10q25-10q26	High and large forehead Flattening of the occipital region Maxillary hypoplasia Exorbitism with hypertelorism Maxillary hypoplasia with mandibular prognathism	Class III occlusion Maxillary dental arch in V shape Spaced teeth Congenital cleft in the palate

on the short arm of the X chromosome (Xp22.3-p22.2)[11] and mutation analysis has identified the gene as *CXORF5*, which was later renamed OFD I as the gene responsible for this disorder.[12] The prevalence of OFD I vary in the literature reports. It is estimated to be between 1 out of 50,000 and 1 out of 250,000 live births[13] it appears to affect all races and ethnicities in equal numbers. Almost all affected individuals are females, as male fetuses with the syndrome die before birth.[14]

The craniofacial features of this syndrome include frontal bossing, facial asymmetry, aplasia of alar cartilage, ocular hypertelorism, strabismus, down slanting palpebral fissures, broadened nasal bridge/root, cleft lip/palate, high arched palate, ankyloglossia, oligodontia, supernumerary teeth, hyperplastic frenula, and micrognathia.[15-17] Malformations of the hands are more common than those of the feet and include the syndactyly, brachydactyly, and clinodactyly.[18] The affected

children may have dry, brittle hair, patches of hair loss and whiteheads, followed by the onset of kidney disease in adult.

Trisomy 13 or Patau syndrome

The classical features of Patau syndrome or trisomy 13 are defects of the auricles, eyes (microphthalmia, iris coloboma, strabismus, etc.), and mouth (cleft lip, palate or both), holoprosencephaly sequence (including arhinencephaly, cebocephaly, and others), hemangiomas, polydactyly, hyperconvex fingernails, scalp defects, and heart defects.[19] Partial duplications for proximal segments (13qll-ql4) alone show some features of Patau syndrome: including strabismus, depressed nasal bridge, stubby nose, cleft lip/palate, clinodactyly, increased polymorphonuclear projections on the segmented neutrophils, and persistence of Hb F.[20]

Trisomy 21 (T21) or Down syndrome

T21 or Down syndrome is the most frequent genetic disorder associated with intellectual disability, affecting between 1.0 and 2.2 of every 1000 live births according to statistics on prenatal testing and selective abortion.[21-24] Because this chromosomal disorder is also associated with various health problems (e.g. hypotonia, congenital heart defects, gastrointestinal diseases) and distinctive physical stigmata (e.g. round face, epicanthal fold, oblique lid axis, flat nasal bridge), persons with T21 are at high risk of being rejected socially.[25]

Turner syndrome

Turner syndrome is a common genetic disorder that has been classically associated with a 45X karyotype, although several other X-chromosomal abnormalities have been identified in these patients, many of which involve mosaicism. It occurs in one out of every 2500 to 3000 female births and is associated with a broad array of potential abnormalities, most of them thought to be caused by haploinsufficiency of genes that are normally expressed by both X chromosomes. Major clinical manifestations include: growth failure, congenital heart disease (e.g. coarctation of the aorta, bicuspid aortic valve, atrial, and ventricular septal defects), gonadal failure, and learning disabilities.[26] Other co-morbidities such as hypothyroidism, diabetes mellitus, deafness, premature osteoporosis, are associated with complex psychosexual factors influenced by hormonal deficiencies and by the disturbed body image due to abnormal physical development.[26,27]

The skeletal characteristics of Turner syndrome are decreased maxillary growth with midface hypoplasia and a wide, micrognathic mandible.[28,29]

Distal molar occlusion (60%), narrow upper arch and wide lower arch with concomitant lateral crossbite (39%) and anterior open bite (17%) are often observed in TS.[30,31] The teeth are smaller than normal,[32] because of reduced enamel thickness with the locus responsible for the reduction of the tooth crown size being reported to be located on the short arm of the X chromosome.[32]

Klinefelter syndrome (KS)

KS describes a sex chromosomal aneuploidy caused by the addition of at least one extra X chromosome to normal male karyotype, XY. It is the most common disorder of sex chromosomes with a prevalence of one in 600 males.[33] Variants of KS are characterized by the addition of an extra X or Y chromosome to classic karyotype 47,XXY. Although somatic malformations and mental retardation are more severe in these variants, most cases remain undiagnosed till puberty when the symptoms of androgen deficiency are recognized.[34,35] The KS patients present with dysmorphic features consisting of hypodontia, hypoplastic teeth, prognathism, short filtrum, gynecomastia, clinodactyly, and fusiform shaped fingers.[36]

Marfan syndrome (MFS)

MFS is an autosomal disease of the connective tissue that is characterized by skeletal anomalies and arachnodactyly.[37] Classic MFS occurs due to a mutation in the FBN1 gene, which codifies for the matrix protein fibrillin, although it is documented that 25% of the sporadic cases lead to de novo mutations in zones, which are distant, several base pairs from this gene sequence.[38]

MFS is often diagnosed in association with other disorders of the connective tissue, such as the Loeys–Dietz syndrome and the Shprintzen–Goldberg syndrome.

The skeletal anomalies are the easiest signs to see[39,40] as flat feet, deep-set eyes, long thin arms, and legs; have loose and flexible joints, tall and slim. MFS can cause the spine to become curved causing backache. Many people with MFS will have some type of vision problem including, myopia, glaucoma, cataracts. However, oral manifestations, such as dental caries and periodontal diseases, although they are common in the general population, also have an increased incidence in patients with the MFS.[41]

Axenfeld-Rieger syndrome (ARS)

ARS is a clinically and genetically heterogeneous disorder with an autosomal dominant mode of transmission and great intrafamilial variability, consisting of a family of developmental diseases including anterior segment abnormalities and a variety of systemic manifestations.[42,43]

ARS can be classified as Axenfeld anomaly (limited to peripheral anterior segment defects), Rieger anomaly (peripheral abnormalities with additional changes in the iris), and Rieger syndrome (ocular anomalies and extraocular developmental defects especially of the teeth, facial bones, and periumbilical skin). Because of the marked genotypic and phenotypic overlap, it has been proposed that these diseases are best considered under the single ARS heading.

These three variations are now recognized as a spectrum of the same syndrome.[42,44] In the literature, cases with ocular and extraocular manifestations are either defined as ARS or Rieger syndrome.[45]

The most important ocular feature of the ARS is glaucoma, which develops in about 50% of affected individuals. The ocular anomalies are suggested to represent an arrest of tissues derived from neural crest cells in gestation.[42]

In ARS, classical signs represented by dental hypoplasia, craniofacial anomalies, and involuted periumbilical skin can be associated with a wide diversity of other traits, such as limb anomalies, short stature, pituitary anomalies, empty sella syndrome, and a variety of neurological, and dermatological disorders.[42,44]

Pycnodysostosis (the Toulouse-Lautrec syndrome)

Pycnodysostosis is a rare autosomal-recessive disorder of osteoclast dysfunction due to mutation of cathepsin K gene[46] causing osteosclerosis. The disease shows equal sex distribution with high parental consanguinity, having an incidence of 1.7 per 1 million births.[47,48] This disorder is characterized by short stature, increased bone density, short and stubby fingers, fragile bones that may fracture easily, and craniofacial abnormalities caused by delayed suture closure. Patients usually present with frequent fractures even after minor trauma.[49]

Apert syndrome

Apert syndrome (Mendelian inheritance in man #101200) represents approximately 5% of all craniosynostosis syndromes.[50,51] This disorder is characterized by severe craniosynostosis, craniofacial abnormalities, and symmetric syndactyly of the hands and feet.[52] Among the craniofacial alterations are the brachycephaly, midface hypoplasia, flat occiput, hypertelorism, proptosis and a short, broad nose with a bulbous tip.[53] The configuration of the palate is characterized by an arched palate with bilateral swellings of the palatine processes, resulting in a pseudo-cleft in the midline.[53,54] Other frequent oral findings include hypotonic lips, bifid uvula, delayed or ectopic eruption, and malocclusion.[55,56] The oral cavity is characterized by impaction, severe crowding, delayed eruption, thick gingiva, sometimes supernumerary teeth, or genetically missing teeth. Other frequent oral cavity findings include Class III malocclusion, anterior open bite, bilateral posterior cross-bite and unilateral posterior crossbite, but to a lesser degree and a midline deviation.

Crouzon syndrome (CS)

CS is an autosomal dominant genetic disease with an incidence of 1 in 25,000 births. The mutation in the genes that codify receptor two of the fibroblast growth factor 2, which is mapped to chromosome locus 10q25-10q26 is responsible for the deformities observed.[57,58]

Extraoral manifestations include a high and large forehead, with the convexity in the region of the anterior fontanelle, flattening of the occipital region and maxillary hypoplasia which are responsible for the appearance of the patient. The clinical features have wide phenotypic variability and consist of bicoronal craniosynostosis, exorbitism with hypertelorism, maxillary hypoplasia with mandibular prognathism, and normal intelligence.

Intraoral features include Class III occlusion and maxillary dental arch in V shape with spaced teeth, congenital cleft in the palate.

Conclusion and Significance

Within this search-review, 10 genetic conditions were described with oral and craniofacial signs that can help forensic specialist in human identification. The first part showed a correlation between genetics, facial signs, and intra-oral signs that would help forensic odontologist in the identification procedures. A second part is underwriting that will evaluate the relation between genetic conditions, oral/craniofacial, and general clinical signs.

References

1. Sengupta S, Sharma V, Gupta V, Vij H, Vij R, Prabhat K. Forensic odontology as a victim identification tool in mass disasters: A feasibility study in the Indian scenario. J Forensic Dent Sci 2014;6(1):58-61.
2. Saxena S, Sharma P, Gupta N. Experimental studies of forensic odontology to aid in the identification process. J Forensic Dent Sci 2010;2(2):69-76.
3. Avon SL. Forensic odontology: The roles and responsibilities of the dentist. J Can Dent Assoc 2004;70(7):453-8.
4. Neville B, Douglas D, Allen CM, Bouquot J. Forensic dentistry. In: Oral and Maxillofacial Pathology, 2nd ed. Philadelphia, PA: W.B. Saunders Co.; 2002. p. 763-83.
5. Kumar A, Ghosh S, Logani A. Occurrence of diversity in dental pattern and their role in identification in Indian population: An orthopantomogram based pilot study. J Forensic Dent Sci 2014;6(1):42-5.
6. Murugesh M, Ganesh SS. Denture labeling in forensic dentistry. J Forensic Dent Sci 2014;6(1):67-9.
7. Colvenkar SS. Lenticular card: A new method for denture identification. Indian J Dent Res 2010;21(1):112-4.
8. Nuzzolese E, Marcario V, Di Vella G. Incorporation of radio frequency identification tag in dentures to facilitate recognition and forensic human identification. Open Dent J 2010;4:33-6.
9. Suri M. Craniofacial syndromes. Semin Fetal Neonatal Med 2005;10(3):243-57.
10. Papillon-Leage E, Psaume J. An inherited malformation of the oral mucosa flanges and abnormal frena: Generalities. Revue de Stomatologie 1954;55(4):209-27.
11. Feather SA, Woolf AS, Donnai D, Malcolm S, Winter RM. The oral-facial-digital syndromes type I (OFDI), a cause of polycystic kidney disease and associated

malformation, maps to Xp22.2-Xp22.3. Hum Mol Genet 1997;6(7):1163-7.
12. Ferrante MI, Giorgio G, Feather SA, Bulfone A, Wright V, Ghiani M, *et al.* Identification of the gene for oral-facial-digital type I syndrome. Am J Hum Genet 2001;68(3):569-76.
13. Shaw M, Gilkes JJ, Nally FF. Oral facial digital syndrome-case report and review of the literature. Br J Oral Surg 1981;19(2):142-7.
14. Rimoin DL, Edgerton MT. Genetic and clinical heterogeneity in the oral-facial-digital syndromes. J Pediatr 1967;71(1):94-102.
15. Gorlin RJ, Psaume J. Orodigitofacial dysostosis – a new syndrome. A study of 22 cases. J Pediatr 1962;61:520-30.
16. King NM, Sanares AM. Oral-facial-digital syndrome, Type I: A case report. J Clin Pediatr Dent 2002;26(2):211-5.
17. Gillerot Y, Heimann M, Fourneau C, Verellen-Dumoulin C, Van Maldergem L. Oral-facial-digital syndrome type I in a newborn male. Am J Med Genet 1993;46(3):335-8.
18. Harrod MJ, Stokes J, Peede LF, Goldstein JL. Polycystic kidney disease in a patient with the oral-facial-digital syndrome - type I. Clin Genet 1976;9:183-6.
19. Helali N, Iafolla AK, Kahler SG, Qumsiyeh MB. A case of duplication of 13q32-+qter and deletion of 18p11.32-+pter with mild phenotype: Patau syndrome and duplications of 13q revisited. J Med Genet 1996;33(7):600-2.
20. Tharapel SA, Lewandowski RC, Tharapel AT, Wilroy RS JR. Phenotype-karyotype correlation in patients trisomic for various segments of chromosome 13. J Med Genet 1986;23(4):310-5.
21. Julian-Reynier C, Aurran Y, Dumaret A, Maron A, Chabal F, Giraud F, *et al.* Attitudes towards Down's syndrome: Follow up of a cohort of 280 cases. J Med Genet 1995;32(8):597-9.
22. Olsen CL, Cross PK, Gensburg LJ. Down syndrome: Interaction between culture, demography, and biology in determining the prevalence of a genetic trait. Hum Biol 2003;75(4):503-20.
23. Murthy SK, Malhotra AK, Mani S, Shara ME, Al-Rowaished EE, Naveed S, *et al.* Incidence of Down syndrome in Dubai, UAE. Med Princ Pract 2007;16(1):25-8.
24. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: Analysis of data from the National Down syndrome cytogenetic register. BMJ 2009;339:b3794.
25. Enea-Drapeau C, Carlier M, Huguet P. Tracking subtle stereotypes of children with trisomy 21: From facial-feature-based to implicit stereotyping. PLoS One 2012;7(4):e34369.
26. Rosenfeld RG, Tesch LG, Asch R, Cara J, Conte F, Hall JG, *et al.* Recommendations for diagnosis, treatment, and management of individuals with turner syndrome. Endocrinologist 1994;4(5):351-8.
27. Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, *et al.* Recommendations for the diagnosis and management of turner syndrome. J Clin Endocrinol Metab 2001;86(7):3061-9.
28. Collett-Solberg PF, Gallicchio CT, Coelho SC, Siqueira RA, Alves ST, Guimarães MM. Endocrine diseases, perspectives and care in turner syndrome. Arq Bras Endocrinol Metabol 2011;55(8):550-8.
29. Davenport ML. Approach to the patient with turner syndrome. J Clin Endocrinol Metab 2010;95(4):1487-95.
30. Laine T, Alvesalo L. Size of the alveolar arch of the mandible in relation to that of the maxilla in 45, X females. J Dent Res 1986;65(12):1432-4.
31. Szilágyi A, Keszthelyi G, Nagy G, Madléna M. Oral manifestations of patients with turner syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89(5):577-84.
32. Midtbø M, Wisth PJ, Halse A. Craniofacial morphology in young patients with turner syndrome. Eur J Orthod 1996;18(3):215-25.
33. Visootsak J, Aylstock M, Graham JM Jr. Klinefelter syndrome and its variants: An update and review for the primary pediatrician. Clin Pediatr Phila 2001;40(12):639-51.
34. Abramsky L, Chapple J. 47, XXY Klinefelter syndrome and 47, XYY: Estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn 1997;17(4):363-8.
35. Linden MG, Bender BG, Robinson A. Sex chromosome tetrasomy and pentasomy. Pediatrics 1995;96:672-82.
36. Purnak S, Ada S, Güleç AT, Balci TB, Sahin FI. Diagnosis of variant klinefelter syndrome in a 21-year-old male who presented with sparse facial hair. Ann Dermatol 2012;24:368-9.
37. Marfan AB. A case of congenital deformation of the four members more pronounced at the ends characterized by the lengthening of bones with some degree of thinning. Bull Mem Soc Med Hop 1896;13:220–6.
38. Loeys B, De Backer J, Van Acker P, Wettinck K, Pals G, Nuytinck L, *et al.* Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. Hum Mutat 2004;24(2):140-6.
39. Pirinen S. Genetic craniofacial aberrations. Acta Odontol Scand 1998;56(6):356-9.
40. Ha HI, Seo JB, Lee SH, Kang JW, Goo HW, Lim TH, *et al.* Imaging of Marfan syndrome: Multisystemic manifestations. Radiographics 2007;27(4):989-1004.
41. Goodman T. Marfan's syndrome. A personal perspective. AORN J 1986;43(2):452-5.
42. Shields MB. Axenfeld-Rieger syndrome: A theory of mechanism and distinctions from the iridocorneal endothelial syndrome. Trans Am Ophthalmol Soc 1983;81:736-84.
43. Pearce WG, Wyatt HT, Boyd TA, Ombres RS, Salter AB. Autosomal dominant iridogoniodysgenesis: Genetic features. Can J Ophthalmol 1983;18(1):7-10.
44. Shields MB. Axenfeld-Rieger and iridocorneal endothelial syndromes: Two spectra of disease with striking similarities and differences. J Glaucoma 2001;105 Suppl 1:S36-8.
45. Perveen R, Lloyd IC, Clayton-Smith J, Churchill A, van Heyningen V, Hanson I, *et al.* Phenotypic variability and asymmetry of Rieger syndrome associated

with PITX2 mutations. Invest Ophthalmol Vis Sci 2000;41(9):2456-60.
46. Krane SM, Schiller AL. Hyperostosis, fibrous dysplasia, and other dysplasias of bone and cartilage. In: Fauci AS, Braunwald E, Isselbacher KJ, Petersdorf RG, Wilsone JD, Martin JB, (Editors). Harrison's Principles of Internal Medicine, New York, NY, USA: McGraw-Hill; 1998. p. 2269-75.
47. Fleming KW, Barest G, Sakai O. Dental and facial bone abnormalities in pyknodysostosis: CT findings. Am J Neuroradiol 2007;28(1):132-4.
48. Mujawar Q, Naganoor R, Patil H, Thobbi AN, Ukkali S, Malagi N. Pycnodysostosis with unusual findings: A case report. Cases J 2009;2:6544.
49. Park WJ, Theda C, Maestri NE, Meyers GA, Fryburg JS, Dufresne C, *et al.* Analysis of phenotypic features and FGFR2 mutations in Apert syndrome. Am J Hum Genet 1995;57(2):321-8.
50. Cohen MM Jr, Kreiborg S, Lammer EJ, Cordero JF, Mastroiacovo P, Erickson JD, *et al.* Birth prevalence study of the Apert syndrome. Am J Med Genet 1992;42(5):655-9.
51. Cohen MM Jr, Kreiborg S. A clinical study of the craniofacial features in Apert syndrome. Int J Oral Maxillofac Surg 1996;25(1):45-53.
52. Cunningham ML, Seto ML, Ratisoontorn C, Heike CL, Hing AV. Syndromic craniosynostosis: From history to hydrogen bonds. Orthod Craniofac Res 2007;10(2):67-81.
53. Paravatty RP, Ahsan A, Sebastian BT, Pai KM, Dayal PK. Apert syndrome: A case report with discussion of craniofacial features. Quintessence Int 1999;30(6):423-6.
54. Tosun G, Sener Y. Apert syndrome with glucose-6-phosphate dehydrogenase deficiency: A case report. Int J Paediatr Dent 2006;16(3):218-21.
55. Letra A, de Almeida AL, Kaizer R, Esper LA, Sgarbosa S, Granjeiro JM. Intraoral features of Apert's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(5):e38-41.
56. Eswarakumar VP, Horowitz MC, Locklin R, Morriss-Kay GM, Lonai P. A gain-of-function mutation of Fgfr2c demonstrates the roles of this receptor variant in osteogenesis. Proc Natl Acad Sci U S A 2004;101(34):12555-60.
57. Reardon W, Winter RM, Rutland P, Pulleyn LJ, Jones BM, Malcolm S. Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. Nat Genet 1994;8(1):98-103.
58. Reardon W, Winter RM, Rutland P, Pulleyn LJ, Jones BM, Malcolm S. Mutations in the ibroblast growth factor receptor 2 gene cause Crouzon syndrome. Nat Genet 1994;8(1):98-103.