Novel Gene Mutations Associated with Crouzon Syndrome

D.Angel Fastina Mary

[1]Research Associate, Dental Research Cell, [2]Assistant Professor, Department of Microbiology, [3]Lecturer, Department of General Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical And Technical Sciences, Saveetha University, Chennai, India

Abstract

Crouzon syndrome exhibits consideration of phenotypic heterogeneity, within the aetiology of which genetics play a crucial role. The *FGFR2* gene mediates extracellular signals into cells and mutations within the *FGFR2* gene cause Crouzon syndrome. The review summarizes the genetic phenotype study and genetic evaluation related to Crouzon syndrome (CS) which frequently determines the degree of complexity, guide management, guidance and intervention related to this craniofacial defect. CS is a disorder characterized by early fusion of certain skull bones (craniosynostosis). This prevents normal growth of the skull, which may affect the form of the top and face. Signs and symptoms of Crouzon syndrome may include wide-set, bulging eyes; strabismus (misalignment of the eyes); "beak-shaped" nose; and an underdeveloped upper jawbone. Other features may include dental problems, deafness, and/or harelip and palate. The severity of signs and symptoms can vary among affected people, even within a family. Intelligence is typically normal, but intellectual disability could also be present. Crouzon syndrome is caused by changes (mutations) within the *FGFR2* gene and is inherited in an autosomal dominant manner. Treatment may involve surgeries to stop complications, improve function, and aid in healthy psychosocial development.

Keywords: *Crouzon syndrome; genotype; molecular pathology; phenotype.*

Introduction

Craniosynostosis is a birth defect characterized by premature fusion of one more of the calvarial sutures before the complications of brain growth and development, leading to restricted growth of the skull, brain, face and central nervous system development[1]. Among craniosynostosis are valued to comprise 15% of all cases. Crouzon syndrome (CS) is a genetic disorder characterized by the premature fusion of certain skull bones (craniosynostosis)[2]. Many features of CS result from the premature fusion of the skull bones. Abnormal growth of those bones results in wide-set, bulging eyes and vision problems caused by shallow eye sockets; eyes that don't point within the same direction (strabismus); a beaked nose; and an underdeveloped upper jaw. In addition, people with CS[3] may have dental problems and hearing loss, which is sometimes accompanied by narrow ear canals. A few of the CS patients have an opening in the lip and at the root of the mouth[4]. The severity of those signs and symptoms varies among affected people. Individuals with Crouzon syndrome usually have normal intelligence [5,6].

Frequency of CS is seen in about 16 per million newborns. It is the most common craniosynostosis syndrome. Crouzon syndrome cs is a most commonly seen syndrome. It is a genetic disorder related to multiple fibroblast growth factor receptor 2 (*FGFR2*) mutations[7,8]. *FGFR2* modulates the extracellular signals into the cells and several mutations in the *FGFR2* gene have been associated with CS. *FGFR2* along with the other genes of the family *FGFR, FGFR1* and *FGFR3* are related to signaling function in cranial sutures and play a crucial role in embryonic development of the limbs[9].

Corresponding author:
J. Vijayashree Priyadharshini.J
Assistant Professor, Department of Microbiology,
Saveetha dental college and Hospitals,
Saveetha Institute of Medical And Technical Sciences
Chennai, India,
Email Id : vijayashreej.sdc@saveetha.com
Ph: 9941125984

This syndrome was first reported by Louis Edouard octave crouzon in 1912 when a triad of Calabrian deformations with craniofacial dysostosis, exophthalmos and facial anomalies was defined in a mother and her son[10]. Inheritance pattern of this condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.[11]

Materials and Methods

By reviewing various available studies, datas were collected through search engines, PubMed, google scholar, journals. The period of duration consideration of collected articles from 2000 - 2020. The dependent variables involved in this were about gene mutations associated with Crouzon syndrome.

Inclusion Criteria :

- Crouzon syndrome prevalence
- Novel mutations associated
- Pathways involved
- Pattern of inheritance
- Management of cs

Exclusion Criteria :

- other than crouzon syndrome were excluded from this study.

Normal Function *FGFR2* Gene :

The *FGFR2* gene encoded for a protein known as the fibroblast growth factor receptor 2 (FGFR2).[12] Fibroblast growth factor receptors governs the processes of cell growth and division (proliferation), cell maturation (differentiation), formation of blood vessels (angiogenesis), wound healing, and embryonic development.[13,14] The FGFR2 protein serves in the outer membrane of cells which are characterized by an extracellular, transmembrane and an intracellular domain.[15] Such a positioning allows the FGFR2 protein to bind to specific growth factors from outside the cell and transduce the signals which aids the cell to respond to its environment. The FGFR2 protein plays a crucial role in the development of bones before birth (embryonic development).[16] Early signals by the protein directs immature cells in the developing embryo to become bone cells and form the head, hands, feet, and other tissues.[17] Several isoforms of the FGFR proteins have also been identified in different tissues, whose patterns may change throughout growth and development.[18] The cytogenetic location of *FGFR* gene is 10q26.13.

Clinical Report of Crouzon Syndrome:

The first description about CS was given by Crouzon in 1912, who described it as a hereditary syndrome or craniofacial dysostosis in a mother and son. He described the calvarial deformities, facial anomalies, and exophthalmos. CS is characterized by premature closure of calvaria and cranial base sutures also as those of the orbit and maxillary complex (craniosynostosis). Other clinical features include hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, hypoplastic maxilla, and relative mandibular prognathism. Prevalence is 1 per 60,000 (approximately 16.5 per 1,000,000) live births. CS makes up approximately 4.8% of all cases of craniosynostosis.[19]

Genetics or Basic Defects Involved in Crouzon Syndrome

Inheritance:

CS is inherited in an autosomal dominant manner. This means that having a change mutation in just one copy of the responsible gene in each cell is enough to cause features of the condition. There is nothing that either parent can do, before or during a pregnancy, to cause a toddler to change state with CS. In some cases, an affected person inherits the mutated gene from an affected parent. In other cases, the mutation occurs for the primary time during a person with no case history of the condition. This is called a de novo mutation. When an individual with a mutation that causes an autosomal dominant condition has children, each child features a 50% (1 in 2) chance to inherit that mutation.[20]

Pathophysiology:

Premature synostosis of the coronal, sagittal, and occasional lambdoidal Suture. begins in the first year of life completed by the second or third year. Degree of deformity and disability determined by the order and rate of suture fusion. After fusion of a suture growth perpendicular to that suture becoming restricted. fused

bones acting as a single bony structure. Compensatory growth occurring at the remaining open sutures to allow Continued brain growth Multiple sutural synostosis often extend to premature fusion of the skull Base sutures causing the following effects such as midfacial hypoplasia, shallow orbit, a foreshortened nasal dorsum, maxillary hypoplasia,occasional upper airway.[21,22] Several *in vitro* studies carried out in our institution formed the basis for the present review on Crouzon syndrome.[23–36]

Recent Gene Mutations Associated With Crouzon Syndrome :

A plethora of mutations have been identified in several genes with close association with craniosynostosis. A case study reported by Luong et al., on a Vietnamese family of three generations identified a heterozygous *FGFR2* missense mutation (c.1012G>C, p.G338R) which was proposed to have been the candidate gene mutation associated with CS. The mutation was further screened in about 200 unrelated control subjects from the same population. The entire coding region or exon 10 of the *FGFR2* gene was amplified and sequenced. The heterozygous mutation was identified only in the patient with CS, while the other family members or controls did not show any such mutations in their gene. In addition to it a novel heterozygous mutation in the exon 11 of FGFR2 was seen in the CS patient which was considered to be a silent mutation.[39] In a case study reported by Korakavi et al., biallelic loss-of-function variant in the interleukin receptor 11 alpha gene (IL11RA) was identified in a patient with Crouzon-like craniosynostosis syndrome with associated dental anomalies. A total of six missense mutations were identified of which four were found to be novel, including 2 in the Ig-like C2-type domain.[37]

Similarly Keupp et al., [38]demonstrated that mutations in the *IL11RA* gene caused an autosomal recessive Crouzon-like craniosynostosis. The homozygosity mapping procedure followed by targeted next-generation sequencing identified a c.479+6T>G mutation in the interleukin 11 receptor alpha gene (IL11RA) on chromosome 9p21 in a family from Antakya, Turkey. The patients presented with features such as multiple suture synostosis, midface hypoplasia, variable degree of exophthalmos, relative prognathism, a beaked nose, and conductive hearing loss. [39]The segregation of mutations were further identified in five families: a German patient of Turkish origin and a Turkish family with three affected sibs all of whom were homozygous for the previously identified *IL11RA* c.479+6T>G mutation; a family with pansynostosis with compound heterozygous missense mutations, p.Pro200Thr and p.Arg237Pro; and two further Turkish families with Crouzon-like syndrome carrying the homozygous nonsense mutations p.Tyr232 and p.Arg292[40].

A report by Nur et al.,demonstrated several mutations in a cluster of patients with different craniosynostosis syndromes. Mis-sense mutations which leads to the substitution of one amino acid to the other viz., p.Trp290Arg, p.Cys342Tyr, p.Cys278Phe, p.Gln289Pro were identified along with a novel p.Tyr340Asn mutation. Ohishi et al., [41]reported a novel mutation in the *FGFR2* gene (p.Asn549Thr) in a CS patient. The team also identified p.Ser252Leu mutation is a CS patient who had phenotypically normal father. The evidence gathered through the present review of literature clearly identifies the *FGFR* family of genes playing a crucial role in craniofacial development.[42,43,44]

Conclusion

The advent of advanced molecular techniques have aided in understanding the genetic basis of craniofacial disorders. The genotype analysis in connection with a disease phenotype is required for proper evaluation of the diseases, to determine the pattern of inheritance and to ascertain the degree of complexity of the disorder. A clear outline about the genetic disorder would further help the clinicians to guide the process of disease management by providing genetic counseling and start with an appropriate treatment intervention.

Acknowledgement : We thank saveetha dental college and Hospitals for the support to carry out this study.

Conflict of Interest: None

Source of Funding : Self

Ethical Clearance: Not Required

References

[1] Schaefer F, Anderson C, Can B, Say B. Novel

mutation in the FGFR2 gene at the same codon as the Crouzon syndrome mutations in a severe Pfeiffer syndrome type 2 case. American Journal of Medical Genetics 1998;75:252–5. https://doi.org/3.0.co;2-s">10.1002/(sici)1096-8628(19980123)75:3<252::aid-ajmg4>3.0.co;2-s.

[2] Maajida Aafreen, M., Geetha, R.V., Thangavelu, L., Evaluation of anti- inflammatory action of laurus nobilis-an in vitro study, International Journal of Research in Pharmaceutical Sciences, vol10(2),1209-1213 https://paperpile.com/c/GTraUD/xd6e (accessed June 15, 2020).

[3] Vaishali, M., Geetha, R.V., Antibacterial activity of orange peel oil on Streptococcus mutans and enterococcus- an in-vitro study, Research Journal of Pharmacy and Technology, vol 11(2) 513- 514 https://paperpile.com/c/GTraUD/xd6e (accessed June 15, 2020).

[4] Pratha AA, Ashwatha Pratha A, Geetha RV. Awareness on Hepatitis-B vaccination among dental students-A Questionnaire Survey. Research Journal of Pharmacy and Technology 2017;10:1360. https://doi.org/10.5958/0974-360x.2017.00240.2.

[5] Gupta P, Rao K. Crouzon Syndrome. Pediatric Dentistry for Special Child 2016:311–311. https://doi.org/10.5005/jp/books/12882_23.

[6] Vavro H. Crouzon Syndrome. Neuroradiology - Expect the Unexpected 2018:95–8. https://doi.org/10.1007/978-3-319-73482-8_13.

[7] Inserm, INSERM. Crouzon syndrome-acanthosis nigricans syndrome. Definitions 2020. https://doi.org/10.32388/w7ubsh.

[8] Steinberger D, Mulliken JB, Müller U. Crouzon syndrome: Previously unrecognized deletion, duplication, and point mutation within FGFR2 gene. Human Mutation 1996;8:386–90. https://doi.org/3.0.co;2-z">10.1002/(sici)1098-1004(1996)8:4<386::aid-humu18>3.0.co;2-z.

[9] Ravine D. Medical genetics: advances in brief: Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. Journal of Medical Genetics 1994;31:895–895. https://doi.org/10.1136/jmg.31.11.895-b.

[10] Stavropoulos D, Hallberg U, Mohlin B, Hagberg C. Living with Crouzon syndrome: how do young adults with Crouzon syndrome handle their life situation? International Journal of Paediatric Dentistry 2011;21:35–42. https://doi.org/10.1111/j.1365-263x.2010.01079.x.

[11] Gaougaou G, Ben-Fadhel Y, Déziel E, Lacroix M. Effect of β-lactam antibiotic resistance gene expression on the radio-resistance profile of E. coli O157:H7. Heliyon 2018;4:e00999. https://doi.org/10.1016/j.heliyon.2018.e00999.

[12] Teven CM, Farina EM, Rivas J, Reid RR. Fibroblast growth factor (FGF) signaling in development and skeletal diseases. Genes Dis 2014;1:199–213.

[13] Li X-Y, Tao H, Jin C, Du Z-Y, Liao W-F, Tang Q-J, et al. Cordycepin inhibits pancreatic cancer cell growth in vitro and in vivo via targeting FGFR2 and blocking ERK signaling. Chin J Nat Med 2020;18:345–55.

[14] Institute NC, National Cancer Institute. FGFR2 Gene. Definitions 2020. https://doi.org/10.32388/24p3ej.

[15] Nur BG, Pehlivanoğlu S, Mıhçı E, et al. Clinicogenetic study of Turkish patients with syndromic craniosynostosis and literature review. Pediatr Neurol. 2014;50(5):482-490. doi:10.1016/j.pediatrneurol.2014.01.023. https://paperpile.com/c/GTraUD/ChtX (accessed June 29, 2020).

[16] Yang J, Tao T, Liu H, Hu Z-L. Inherited FGFR2 mutation in a Chinese patient with Crouzon syndrome and luxation of bulbus oculi provoked by trauma: a case report. BMC Ophthalmol 2019;19:209.

[17] Lin M, Lu Y, Sui Y, Zhao N, Jin Y, Yi D, et al. Extremely severe scoliosis, heterotopic ossification, and osteoarthritis in a three-generation family with Crouzon syndrome carrying a mutant c.799T>C FGFR2. Mol Genet Genomic Med 2019;7:e843.

[18] FGFR2 mutation in a Chinese family with unusual Crouzon syndrome. International Journal of Ophthalmology 2016. https://doi.org/10.18240/ijo.2016.10.06.

[19] Rollnick BR. Germinal mosaicism in Crouzon syndrome [Internet]. Vol. 33, Clinical Genetics. 2008. p. 145–50. Available from: http://dx.doi.org/10.1111/j.1399-0004.1988.tb03429.x (accessed June 29, 2020).

[20] Cohen MM, Michael Cohen M, Krelborg S. Birth prevalence studies of the Crouzon syndrome: comparison of direct and indirect methods [Internet]. Vol. 41, Clinical Genetics. 2008. p. 12–5. Available from: http://dx.doi.org/10.1111/j.1399-0004.1992.tb03620.x (accessed June 29, 2020).

[21] Abu-Sittah GS, Jeelani O, Dunaway D, Hayward R. Raised intracranial pressure in Crouzon syndrome: incidence, causes, and management. J Neurosurg Pediatr. 2016;17:469-475. https://www.ncbi.nlm.nih.gov/pubmed/26613275 (accessed June 3, 2020).

[22] Priyadharsini JV, Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. An insight into the emergence of Acinetobacter baumannii as an oro-dental pathogen and its drug resistance gene profile – An in silico approach [Internet]. Vol. 4, Heliyon. 2018. p. e01051. Available from: http://dx.doi.org/10.1016/j.heliyon.2018.e01051 (accessed June 29, 2020).

[23] Sivakumar S, Smiline Girija AS, Vijayashree Priyadharsini J. Evaluation of the inhibitory effect of caffeic acid and gallic acid on tetR and tetM efflux pumps mediating tetracycline resistance in Streptococcus sp., using computational approach [Internet]. Vol. 32, Journal of King Saud University - Science. 2020. p. 904–9. Available from: http://dx.doi.org/10.1016/j.jksus.2019.05.003 (accessed June 29, 2020).

[24] Hagberg CA. Benumof and Hagberg's Airway Management E-Book. Elsevier Health Sciences; 2012.

[25] Anderson PJ, Hall CM, Evans RD, Jones BM, Harkness W, Hayward RD. Cervical Spine in Pfeiffer's Syndrome [Internet]. Vol. 7, Journal of Craniofacial Surgery. 1996. p. 275–9. Available from: http://dx.doi.org/10.1097/00001665-199607000-00005 (accessed June 29, 2020).

[26] Priyadharsini JV, Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species [Internet]. Vol. 94, Archives of Oral Biology. 2018. p. 93–8. Available from: http://dx.doi.org/10.1016/j.archoralbio.2018.07.001 (accessed June 29, 2020).

[27] Ushanthika T, Smiline Girija AS, Paramasivam A, Vijayashree Priyadharsini J. An in silico approach towards identification of virulence factors in red complex pathogens targeted by reserpine [Internet]. Natural Product Research. 2019. p. 1–6. Available from: http://dx.doi.org/10.1080/14786419.2019.1641811 (accessed June 29, 2020).

[28] Shahzan MS, Sohaib Shahzan M, Smiline Girija AS, Vijayashree Priyadharsini J. A computational study targeting the mutated L321F of ERG11 gene in C. albicans, associated with fluconazole resistance with bioactive compounds from Acacia nilotica [Internet]. Vol. 29, Journal de Mycologie Médicale. 2019. p. 303–9. Available from: http://dx.doi.org/10.1016/j.mycmed.2019.100899 (accessed June 29, 2020).

[29] Bennaoui F. EMERGENCE OF NEONATAL NOSOCOMIAL INFECTIONS WITH ACINETOBACTER BAUMANNII [Internet]. Available from: http://dx.doi.org/10.26226/morressier.5b5f433ab56e9b005965b777 (accessed June 29, 2020).

[30] Amino Acid Conjugated Polymers: Antibacterial Agents Effective against Drug-Resistant Acinetobacter baumannii with No Detectable Resistance [Internet]. Available from: http://dx.doi.org/10.1021/acsami.9b09016.s001 (accessed June 29, 2020).

[31] Marickar RF, Geetha RV, Neelakantan P. Efficacy of Contemporary and Novel Intracanal Medicaments againstEnterococcus Faecalis. Journal of Clinical Pediatric Dentistry 2014;39:47–50. https://doi.org/10.17796/jcpd.39.1.wmw9768314h56666.

[32] Shahana RY, Muralidharan NP. Efficacy of mouth rinse in maintaining oral health of patients attending orthodontic clinics. Research Journal of Pharmacy and Technology 2016;9:1991. https://doi.org/10.5958/0974-360x.2016.00406.6.

[33] Selvakumar R, Np M. COMPARISON IN BENEFITS OF HERBAL MOUTHWASHES WITH CHLORHEXIDINE MOUTHWASH: A REVIEW. Asian Journal of Pharmaceutical and Clinical Research 2017;10:3. https://doi.org/10.22159/ajpcr.2017.v10i2.13304.

[34] Renuka, S., & Muralidharan, N. P. (2017, February 1). Comparison in benefits of herbal mouthwashes with chlorhexidine mouthwash: A review. Asian Journal of Pharmaceutical and Clinical Research https://paperpile.com/c/GTraUD/ChtX (accessed June 29, 2020).

[35] Girija ASS, Smiline Girija AS, Vijayashree Priyadharsini J, Paramasivam A. Plasmid-encoded resistance to trimethoprim/sulfamethoxazole mediated by dfrA1, dfrA5, sul1 and sul2 among Acinetobacter baumannii isolated from urine samples of patients with severe urinary tract infection. Journal of Global Antimicrobial Resistance 2019;17:145–6. https://doi.

org/10.1016/j.jgar.2019.04.001.

[36] Ashwin KS, Muralidharan NP. Vancomycin-resistant enterococcus (VRE) vs Methicillin-resistant Staphylococcus Aureus (MRSA). Indian Journal of Medical Microbiology 2015;33:166. https://doi.org/10.4103/0255-0857.150976.

[37] Korakavi N, Prokop JW, Seaver LH. Evolution of the phenotype of craniosynostosis with dental anomalies syndrome and report of IL11RA variant population frequencies in a Crouzon-like autosomal recessive syndrome. Am J Med Genet A. 2019;179(4):668□673. doi:10.1002/ajmg.a.61070 https://paperpile.com/c/GTraUD/or7D (accessed June 11, 2020).

[38] Nagase T, Nagase M, Hirose S, Ohmori K. Crouzon syndrome with acanthosis nigricans: case report and mutational analysis. Cleft Palate Craniofac J 2000;37:78–82.

[39] Ohishi A, Nishimura G, Kato F, et al. Mutation analysis of FGFR1-3 in 11 Japanese patients with syndromic craniosynostoses. Am J Med Genet A. 2017;173(1):157-162. doi:10.1002/ajmg.a.37992 https://paperpile.com/c/GTraUD/ChtX (accessed June 29, 2020).

[40] Girija SAS, Jayaseelan VP, Arumugam P. Prevalence of VIM- and GIM-producing Acinetobacter baumannii from patients with severe urinary tract infection. Acta Microbiologica et Immunologica Hungarica 2018;65:539–50. https://doi.org/10.1556/030.65.2018.038.

[41] Smiline Girija AS, Vijayashree Priyadharsini J, Paramasivam Arumugam. CLSI based antibiogram profile and the detection of MDR and XDR strains of Acinetobacter baumannii isolated from urine samples. Medical Journal of the Islamic Republic of Iran. 2019; 33(3); 11- 16 https://paperpile.com/c/GTraUD/qJpi (accessed June 15, 2020).

[42] Smiline ASG, Vijayashree JP, Paramasivam A. Molecular characterization of plasmid-encoded blaTEM, blaSHV and blaCTX-M among extended spectrum β-lactamases [ESBLs] producing Acinetobacter baumannii. British Journal of Biomedical Science 2018;75:200–2. https://doi.org/10.1080/09674845.2018.1492207.

[43] Ciurea AV, Toader C. Genetics of craniosynostosis: review of the literature. J Med Life 2009;2:5–17.

[44] Prasad M. The Crouzan Syndrome-A Case Report. JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 2013. https://doi.org/10.7860/jcdr/2013/4933.2988.