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ABSTRACT

C**raniosynostosis** describes the premature fusion of one or more of the cranial sutures leading to secondary distortion of skull shape because of a combination of lack of growth perpendicular to the fused suture and compensatory overgrowth at the non-fused sutures. Craniosynostosis can be divided into isolated or syndromic type and non-syndromic type. Left untreated, craniosynostosis can result in worsened cranial deformity and, potentially, overall cranial growth restriction with resultant increased ICP. Because of the risks associated with untreated craniosynostosis, it is usually treated surgically soon after diagnosis.

KEYWORDS: craniosynostosis, fusion, isolated, restriction, surgical.

CRANIOSYNOSTOSIS

Bones provide support for our bodies and help form our shape. There are 206 bones in an adult body. The skull of the human being consists of 22 bones out of which 8 are cranial bones and 14 are facial skeleton bones. In the neurocranium these are the occipital bone, 2 temporal bones, 2 parietal bones, the sphenoid, ethmoid and frontal bones.[1] The **cranial vault,** also known as the **skull vault, skullcap** or **calvaria** comprises of 15 sutures, 3 of them are single sutures i.e., coronal, sagittal and lambdoid, and several paired sutures i.e., squamous, spheno-frontal, spheno-squamous, spheno-parietal, parieto-mastoid, and occipito-mastoid.[2]

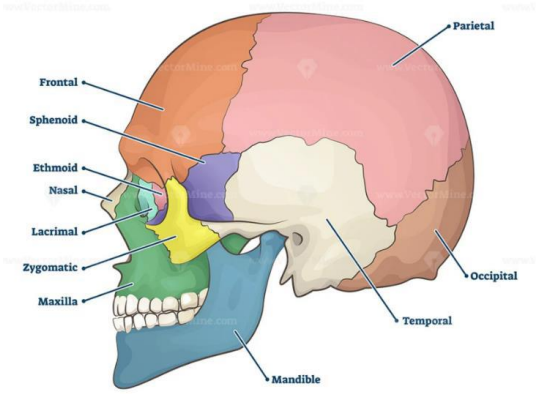

Figure.1: Cranium and its parts[3]

Craniosynostosis, the word is derived from three words; 'carnio' meaning cranium, 'syn' meaning together and 'ostosis' meaning related to bone, is one of the most common craniofacial anomalies. It has a prevalence of 1 in 2250 live births and occurs in all ethnic groups. After orofacial clefts, it is the 2nd most common craniofacial anomaly.[4]

The most commonly used **Clinical Genetic Classification of craniosynostosis** is:

DIAGNOSTIC CATEGORY	NAME OF DISORDER	ETIOLOGY
Isolated craniosynostosis	Morphologically described	Unknown, uterine constraint, or FGFR3 mutation
Syndromic craniosynostosis	Antley-Bixler syndrome	Unknown
	Apert syndrome	Usually one of two common mutation in FGFR3
	Baere- Stevenson syndrome	Mutation in FGFR2 or FGFR3
	Baller- Gerold syndrome	Mutation in TWIST heterogenous
	Carpenter syndrome	Unknown
	Craniofrontonasal dyspasia	Unknown gene atXp22

	Crouzon syndrome	Numerous different mutations in FGFR2
	Crouzonomesodermoskeletal syndrome	Mutations in FGFR3
	Jakson- Weiss syndrome	Mutation in FGFR2
	Muenke syndrome	Mutation in FGFR3
	Pfeiffer syndrome	Mutation in FGFR1 or numerous mutation in FGFR2
	Saethre- Chotzen syndrome	Mutation in TWIST
	Shprintzen- Goldberg syndrome	Mutation in FBN1

Table.1: Clinical Genetic Classification of Craniosynostosis
Reference: Mooney MP, Siegel MI (Eds.). (2002). Understanding Craniofacial Anomalies

When craniosynostosis is the isolated finding in an individual, it is called as **non- syndromic or isolated craniosynostosis.** Most of the times, it is a part of the collection of abnormalities such as Apert, Carpenter or Crouzon syndromes and is called as **syndromic craniosynostosis.**[5] Approximately 92% of craniosynostosis cases are sporadic ones and other family members do not present with any symptoms. In the majority of the cases, the disease is isolated and non-syndromic and, in more severe cases, it might be complicated with increased intracranial pressure, visual impairment, hearing loss, sleep disturbances, choanal atresia, or psychomotor delay with intellectual disability. In syndromic craniosynostoses, the skull deformity is associated with additional clinical symptoms that may include hand and feet malformations, skeletal and cardiac defects, developmental delay and others.[4]

According to **International Society for Pediatric Neurosurgery**, the incidence of non- syndromic cases in children is 1 in 5000 births of sagittal synostosis, 1 in 10,000 births for coronal synostosis, 1 in 7000-15,000 for metopic synostosis and less than 1 in 10,000 births for lambdoidal synostosis.[6] (Figure 2) In India, the incidence of craniosynostosis has been estimated to be 1 in 2,500 live births.[7] The diagnosis of a typical craniosynostosis is usually clinical and it is commonly diagnosed in the 1st year of life.

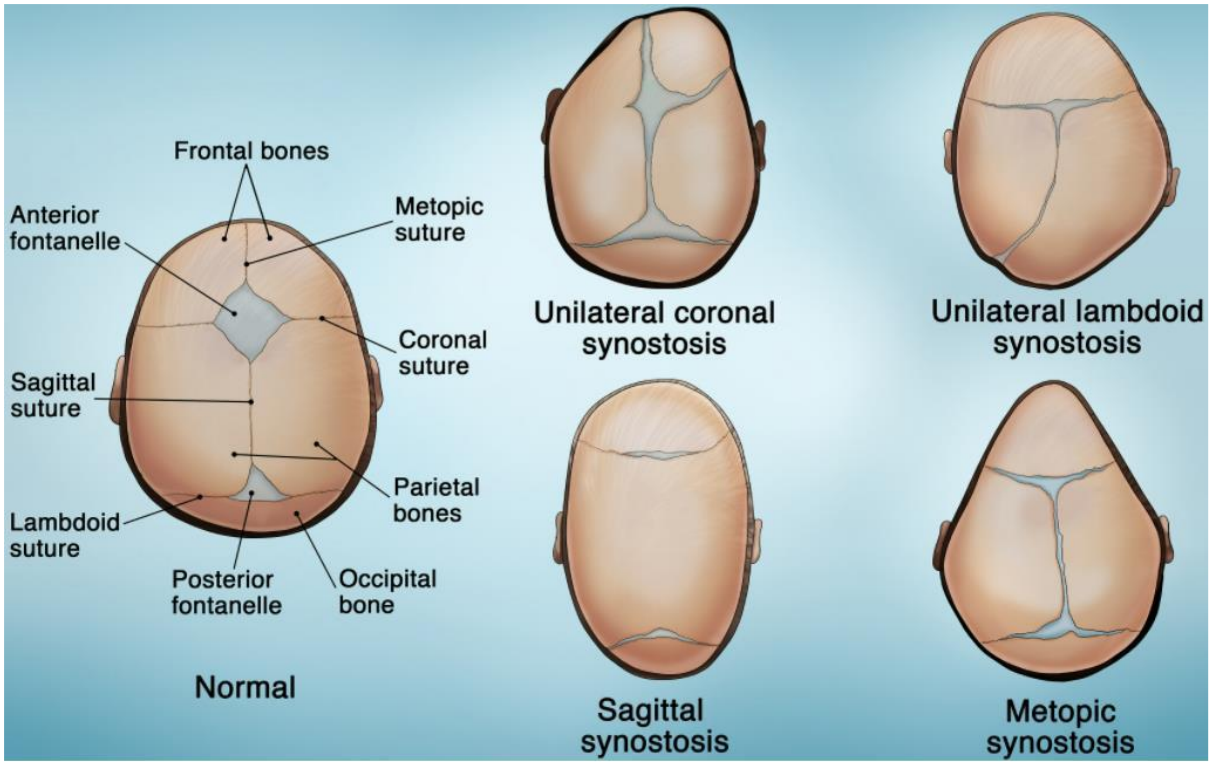

Figure.2: Single suture craniosynstosis

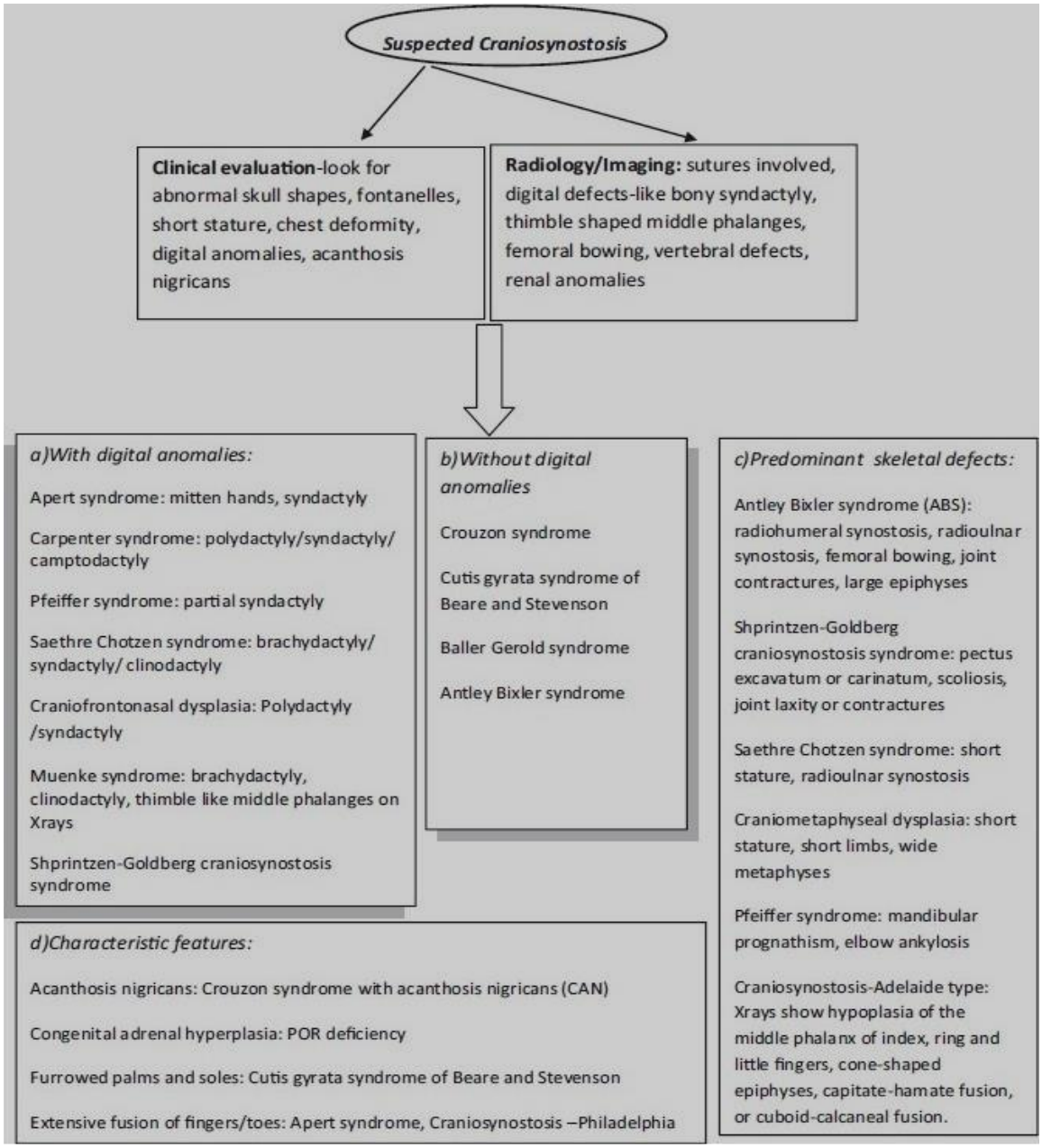

Figure.3: Approach to clinical diagnosis of craniosynostosis syndromes[8]

Currently, the genetic understanding of craniosynostosis is remarkably increasing. Various genetic mutations related to craniosynostosis are identified, e.g., mutations of FGFR, TWIST, MSX2, and EFNB1 gene. Similarly to the underlying causes and clinical characteristics, the treatment of craniosynostoses is also very heterogeneous. Most of the uncomplicated, non-syndromic forms may be treated electively. On the other hand, some cases of the syndromic forms require urgent interventions.[9]

In severe cases, the focus is on maintaining the airway and nutritional support, eye protection and normal ICP. The most important factors in determining the extent of surgery and surgical modalities are the patient's age and presentation. Although the surgical treatment of craniosynostoses is most commonly used, the conservative approach may be adopted first, especially in patients with positional plagiocephaly and in cases where unilateral synostosis is not much pronounced. The main objectives are to achieve a normal brain development by providing sufficient space within the skull and a cosmetically acceptable appearance.[10]

DEVELOPMENT AND GROWTH OF THE CRANIAL VAULT IN CRANIOSYNOSTOSIS

Comprehension of the manifold changes undergone by organ systems during their development will lead to an understanding of the dysmorphology exhibited in many syndromes of congenital anomalies that the clinician is called on to diagnose and treat. As can be seen, there is a wide spectrum of human craniofacial morphologies that are all within the range of normal human variation. This diversity is produced by an interaction of normal genetic and epigenetic factors such as developmental acclimatizations to extreme environment. It has also been suggested that populations with certain morphologies may be predisposed or at risk for craniofacial anomalies based, in part, on facial, palatal, or cranial vault growth rates and morphologies.[11]

Morphogenesis of the bones of the cranial vault is a lengthy developmental process initiated during early embryogenesis and completed during adulthood. First is the embryonic phase; which is the first 8 weeks of pregnancy. In this phase, formation of the cranial vault is preceded by the formation of mesenchymal cells by epithelial-mesenchymal transformation (EMT) via the mesenchymatous or pre-condensation and development of the cranial bones begins with condensation of mesenchymal cells.[12]

Second is the fetal phase which is the interval from the end of the embryonic phase to birth. In this phase, IM ossification for the primitive membranous skull formation begins. And cranial sutures are formed and it plays a critical role as IM bone are growth sites. Also, skull bones grow through displacement and bone remodelling. Characteristic features associated with the development of neurocranium in the embryonic period are collected in the Table 2.

WEEKS	DAYS	EXTERNAL FEATURES
1	1-7	Fertilization
2	8-14	Primitive streak develops
3	15-21	Gastrulation commences and notochordal process forms
		Primitive pit, neural plate, neural groove, neural folds form Somites begin to form
4	22-28	Neural folds fuse, oTic pits form Cranial neuropore closes. Thd first four somites are beginning to be incorporate into the occipital segmentation. Oropharyngeal membrane ruptures, optic vesicles develop, optic pits begin to form
5	29-35	Caudal neuropore closes. Pharyngeal arches 3 and 4 form
		Otic vesicles form. The meninx primitive is first seen as the first signs of the cranial vault. Occipital sclerotomal mesenchyme concentrates around the notochord.
		Cerebral hemispheres become visible
		Sensory and parasympathetic cranial nerve ganglia begin to form
6	36-42	The skull has a membranous roof present
		Cerebellum begins to form. Conversion of the ectomenix mesenchyme into cartilage starts on 40-41 days. Pia mater is present around the brain.
7	43-49	Skeletal ossification begins.
		The first indication of dura mater is found in the skull. Chondrification continues.
8	50-56	By the end of 2nd month (57 days) the endomeninx covers significant portion of the brain and has develop into the arachnoid and the pia mater. Dural reflections begin to form

Table.2: Stages of human embryonic developments (Reference: Development and Growth of the Normal Cranial Vault by SW Jin, et al.)

Sutures are formed during embryonic development at the sites of approximation of the membranous bones of the cranial bones and as a flexible fibrous tissue uniting the adjacent bones. The site of suture formation corresponds to the location of major dural reflections. Dural reflexions are double folding of the meningeal dura which firmly attach the skull base at the crista galli, the cribriform plate, the lesser wings of the sphenoid and the petrous temporal crests. These reflections act as partitions of the cranial cavity under the calvarium, adopting a course that follows the main direction of the sutures.[13] In conjunction with falx cerebri and the tentorium cerebelli, these come

to define the zones where bone growth slows down and the coronal, lambdoid, and sagittal sutures develop. Without the dural bands, the brain would expand as a perfect sphere. By 16 weeks, the radiating centers of ossification have almost reached the sites of reflective bands in the dura. These latter sites remain unossified as regions of connective tissue between the outspreading islands of membranous bone. Once sutures are formed, a second phase of development occurs, in which rapid growth of the cranial bone takes place via the regulated proliferation and differentiation of osteoprogenitor at the periphery of each bone field, which is called the osteogenic front.[14]

Growth of the cranial vault takes place in the following way: 1) increases in width primarily through fill in ossification of the proliferating connective tissue in the interparietal, lambdoidal, parietosphenoidal and parietotemporal sutures. 2) Increase in length may be primarily due to the growth of the cranial base with active response at the coronal suture. 3) Increase in height is due to the activity of the parietal sutures along with the occipital, temporal and sphenoidal contiguous osseous structures.[15]
Premature osseous obliteration of sutures (craniosynostosis) by fusion of bone fronts across the suture site prevents further bone formation at this site. The loss of the sutural growth sites causes an inability to accommodate rapid, expansive growth of the neurocranium, leading to abnormal compensatory morphogenesis throughout the head and typically results in craniofacial dysmorphology.

ETIOLOGIES OF CRANIOSYNOSTOSIS

Craniosynostosis with syndromes is often caused by a genetic alteration. A detectable genetic or environmental cause is more likely if coronal suture or multiple suture synostosis is observed, if a patient shows symptoms of growth or developmental retardation or if a patient shows other congenital anomalies. Unlike syndromic craniosynostosis, isolated craniosynostosis probably is a complex trait, likely arising from a combination of polygenic influences and epigenetic factors i.e. the environmental factors.[16]

The most common craniosynostosis syndromes include the autosomal dominant Crouzon, Apert, and Saethre Chotzen syndromes. The classical clinical descriptions of these three conditions are distinctive. The phenotypic variability of these conditions represents the phenotypic spectrum associated with fibroblast growth receptor 2 (FGFR2) mutations. Pfeiffer, Jackson-Weiss, and Beare-Stevenson syndromes and nonsyndromic coronal craniosynostosis can be caused by mutations in other members of the same receptor family, demonstrating genetic heterogeneity. Saethre-Chotzen and Robinow-Soaurf syndromes are allelic, both with mutations in the TWIST gene that codes for a transcription factor with a DNA binding and helix-loop-helix domains. Other less common craniosynostosis syndromes include craniosynostosis, Boston type, with a mutation in the MSX2 gene that codes for a transcription factor with a homeobox domain.[17] In 2015, a total of 57 human genes were described for which there had been evidence that mutations were causally related to craniosynostosis. These genes can be divided into 2 broad groups. First, a group of 20 genes causing syndromes that are frequently associated with craniosynostosis. Second, a group of genes that cause disorders that are probably causally associated with craniosynostosis but only in a minority of the cases.`[18]

Table 2. Genes recently associated with craniosynostosis[a]

	Gene	OMIM	Location	Clinical disorder	Major phenotypic features	Inheritance pattern	Prevalence of CSO with mutation	First references
1	*ABCC9*	601439	12p12.1	Cantu syndrome	Congenital hypertrichosis, neonatal macrosomia, macrocephaly, coarse facial features, distinct osteochondrodysplasia: thickened calvarium, narrow thorax, wide ribs, flattened or ovoid vertebral bodies, coxa valga, osteopenia, enlarged medullary canals, and metaphyseal widening of long bones Cardiac manifestations: cardiomegaly, patent ductus arteriosus, ventricular hypertrophy, pulmonary hypertension, and pericardial effusions Motor and speech delay	AD	1 patient	Hiraki et al., 2014
2	*AHDC1*	615790	1p36.1p35.3	Xia-Gibbs syndrome	ID, failure to thrive, hypotonia, absent expressive language, OSA, bicoronal suture and metopic suture synostosis, moderate developmental delay, hoarse cry	AD	1 patient with CSO	Miller et al., 2017
3	*CHST3*	603799	10q22.1	Larsen	Short long bones, bilateral clubfeet, micrognathia, scaphocephaly, genu valga, internal rotation of the hips, subluxed hips and elbows, coronal clefting of several vertebral bodies in the lumbar spine and prominent angulation of the lumbar sacral junction, phalangeal bones appeared slightly thickened and spade-like, prominent anterior slip of C2 on C3, lumbar lordosis, mild hypertelorism, slightly prominent metopic ridge, mild temporal hollowing, an anterior placed bregma, and a pinched appearance of the upper ear helix	AR	1 patient	Searle et al., 2014
4	*CRTAP*	605497	3p22.3	Cole-Carpenter syndrome	OI with CSO	AR	1 patient with CSO, others with OI	Balasubramanian et al., 2015
5	*GLIS3*	610192	9p24.2		Neonatal diabetes, thyroid disease, hepatic and renal disease with liver dysfunction, renal cysts, CSO, hiatus hernia, atrial septal defect, splenic cyst, choanal atresia, sensorineural deafness, exocrine pancreatic insufficiency	AR (biallelic)	1 patient	Dimitri et al., 2015
6	*IFT43*	614068	14q24.3	Sensenbrenner syndrome	Sensenbrenner syndrome: skeletal abnormalities (CSO, narrow rib cage, short limbs, brachydactyly), ectodermal defects, renal failure, hepatic fibrosis, heart defects and retinitis pigmentosa	AR	1 patient	Arts et al., 2011
7	*IL6ST*	600694	5q11.2	STAT3 hyper-IgE-like syndrome	Recurrent infections, eczema, bronchiectasis, high IgE, eosinophilia, defective B cell memory, impaired acute-phase response, CSO	AR	1 patient	Schwerd et al., 2017
8	*KANSL1*	612452	17q21.31	Chromosome 17q21.31 deletion syndrome/ Koolen-de Vries syndrome/*KANSL1* haploinsufficiency syndrome	Highly distinctive facial features, moderate-to-severe ID, hypotonia and friendly behavior, epilepsy, heart defects, kidney anomalies, sagittal suture synostosis, macrocephaly, microcephaly	AD	1 patient CSO	Zollino et al., 2015
9	*MED13L*	608771	12q24.21	*MED13L* haploinsufficiency syndrome	ID, developmental delay, congenital heart defects, dysmorphic features, 1× CSO, and microcephaly and macrocephaly	AD	1 patient CSO	Yamamoto et al., 2017
10	*NTRK2*	600456	9q21.33	Hyperphagic obesity associated with developmental delay	Hyperphagia, streak ovaries and uterus, coronal suture synostosis, temper tantrums, speech and language delay	AD	1 patient CSO	Miller et al., 2017
11	*OSTEM1*	607649	6q21	OP	OP, CSO, Chiari I, progressive irritability, abnormal movements, progressive visual loss, global developmental delay, lower motor neuron facial palsy, hydrocephalus	AR	1 patient triad of OP, CSO, and Chiari	Mahmoud Adel et al., 2013
12	*PPP1CB*	600590	2p23.2	*PPP1CB*-related Noonan syndrome with loose anagen hair	Sparse, thin, and slow-growing hair, relative or absolute macrocephaly, prominent forehead, dolichocephaly, ocular hypertelorism, low-set posteriorly angulated ears, developmental delay, learning/behavior problems, short stature, cardiac anomalies, ventriculomegaly, Chiari I, Dandy Walker, CSO	AD	1 patient CSO	Bertola et al., 2017

17	*SLC25A24*	608744	1p13.3	Gorlin-Chaudhry-Moss syndrome and Fontaine syndrome	Coronal CSO, severe midface hypoplasia, body and facial hypertrichosis, microphthalmia, short stature, short distal phalanges, lipoatrophy, and cutis laxa	AD	5 patients	Ehmke et al., 2017; Writzl et al., 2017
18	*SMAD6*	602931	15q22.31	Susceptibility to CSO	Nonsyndromic midline CSO	Complex	Frequent	Timberlake et al., 2016
19	*BMP2*	112261	20p12.3	Susceptibility to CSO	Nonsyndromic midline CSO	Complex	Common SNP	Timberlake et al., 2016
20	*SMO*	601500	7q32.1	Curry-Jones syndrome	Coronal CSO, cutaneous syndactyly, bilateral preaxial polydactyly of the feet, streaky skin lesions, ectopic hair growth, abnormalities of brain development, coloboma and/or microphthalmia, intestinal malrotation and/or obstruction, mild ID	Mosaic mutations	Multiple patients	Twigg et al., 2016
21	*SOX6*	607257	11p15.2		Brachycephaly, proptosis, midfacial hypoplasia, low-set ears, lambdoid suture synostosis, sagittal suture synostosis, gaping anterior fontanelle	AD	1 balanced translocation; 1 SNP	Tagariello et al., 2006
22	*ZNF462*	617371	9q31.2		Ptosis, metopic ridging, CSO, dysgenesis of the corpus callosum, and developmental delay	AD	8 patients	Weiss et al., 2017

[a] Incidence in >1 patient with craniosynostosis. AD, autosomal dominant; ADD, attention deficit disorder; AR, autosomal recessive; CSO, craniosynostosis; ID, intellectual disability; PMR, psychomotor retardation.

Human and animal studies suggest that environmental factors are less likely to play a role in the causation of craniosynostoses, which are frequently Mendelian in inheritance. In reality, it is likely that the majority of environmental factors act in conjunction with genetic factors and other environmental exposures as stochastic events. The different better-known environmental factors linked to craniosynostosis has been divided into the following major groups:

Table 1. Genes recently associated with craniosynostosis[a]

	Gene	OMIM	Location	Clinical disorder	Major phenotypic features	Inheritance pattern	Prevalence of CSO with mutation	First references
1	*B3GAT3*	606374	11q12.3	*B3GAT3*-related disorder	CSO, radioulnar, radiohumeral synostosis	AR	6 patients	Yauy et al., 2018
2	*BRAF*	164757	7q34	Cardiofaciocutaneous syndrome	Cardiofaciocutaneous syndrome with sagittal and/or lambdoid synostosis	AD	4 patients	Ueda et al., 2017
3	*CD96*	606037	3q13.1q13.2	C syndrome/Opitz trigonocephaly	Trigonocephaly, unusual facies, wide alveolar ridges, multiple oral frenula, limb defects, visceral anomalies, redundant skin, PMR, hypotonia	AR (biallelic)	1 balanced translocation that disrupted *CD96* and 1 missense mutation	Chinen et al., 2006; Kanante et al., 2007
4	*DPH1*	603527	17p13.3	3C syndrome-like phenotype	ID, short stature, craniofacial and ectodermal anomalies, scaphocephaly	AR	2 families with deviated skull shape with and without CSO	Loucks et al., 2015
5	*FGF9*	600921	13q12.11		Sagittal suture synostosis, synostoses of interphalangeal, carpal-tarsal, humeroradial, and lumbar vertebral joints	AD	2 families; 1 father and son with CSO	Wu et al., 2009; Rodriguez-Zabala et al., 2017
6	*FTO*	610966	16q12.2		Multiple malformation syndrome: postnatal growth retardation, severe psychomotor delay, functional brain deficits, characteristic facial dysmorphisms (CSO, microcephaly, macrotia, cataract, cryptorchidism)	AR	1 patient with CSO, others have microcephaly or asymmetry of the skull	Boissel et al., 2009
7	*HNRNPK*	600712	9q21.32	Kabuki syndrome/ Au-Kline syndrome	PMR, ADD, dolichocephaly, ridged metopic suture, long face, long palpebral fissures, ptosis, broad or sparse lateral eyebrows, underdeveloped ear helices, wide nasal bridge, open downturned mouth, high palate, prominent midline tongue groove, missing molars, and excess nuchal skin, cryptorchidism, skeletal anomalies, cardiac defects, hypotonia, hyporeflexia, and high pain tolerance	AD	3 patients	Au et al., 2015
8	*IFT140*	614620	16p13.3	C syndrome/Opitz trigonocephaly	Trigonocephaly, unusual facies, wide alveolar ridges, multiple oral frenula, limb defects, visceral anomalies, redundant skin, PMR, hypotonia	AR (biallelic)	3 patients: 1 trigonocephaly, 2 scaphocephaly	Perrault et al., 2012; Peña-Padilla et al., 2017
9	*IGF1R*	147370	15q26.3		Isolated sagittal or coronal CSO	AD	3 patients (associated with)	Cunningham et al., 2011
10	*KAT6B*	605880	10q22.2	Lin-Gettig syndrome-like CSO/genitopatellar syndrome/Say Barber Biesecker Young Simpson syndrome	Multiple malformation syndrome and sagittal suture synostosis	AD	2 patients with CSO	Bashir et al., 2017
11	*MASP1*	600521	3q27.3	3MC syndrome 1	Blepharophimosis, blepharoptosis, epicanthus inversus, developmental defect of the anterior segment of the eye leading to corneal stromal opacities, limitation of upward gaze, cleft lip/palate, minor skeletal abnormalities	AR	At least 2 patients	Urquhart et al., 2016; Munye et al., 2017
12	*NFIA*	600727	1p31.3		Cloverleaf skull, metopic synostosis, macrocephaly, renal and central nervous system malformations, cleft palate, severe ocular anomalies, upslanting palpebral fissures, cutis laxa, developmental delay, seizures, round face with prominent nose, anteverted nares, micro/retrognathia, half-opened mouth, short neck, hand/foot malformations, abnormal external genitalia	AD	4 patients	Rao et al., 2014; Nyboe et al., 2015
13	*P4HB*	176790	17q25.3	Cole-Carpenter syndrome	Osteogenesis imperfecta with CSO	AD	2 patients	Rauch et al., 2015
14	*PTPN11*	176876	12q24.13	Noonan syndrome	Noonan syndrome and sagittal synostosis	AD	3 patients	Ueda et al., 2017
15	*RSPRY1*	616585	16q13	Spondyloepimeta-physeal dysplasia, Faden-Alkuraya type	Progressive spondyloepimetaphyseal dysplasia, short stature, facial dysmorphism, short fourth metatarsals, ID, CSO	AR	4 Saudi sibs, but not in Peruvian patient	Faden et al., 2015
16	*SCN4A*	603967	17q23.3	Congenital myopathy with "corona" fibers, selective muscle atrophy, and CSO	Lower facial weakness, high-arched palate, metopic and sagittal suture synostosis, axial hypotonia, proximal muscle weakness, mild scoliosis, and unusual muscle biopsy: myofibers with internalized nuclei, myofibrillar disarray, and "corona" fibers	AR	2 brothers	Gonorazky et al., 2017

13	*PTPRD*	601598	9p24.1p23	*PTPRD* microdeletion syndrome	Trigonocephaly, scaphocephaly, growth retardation, hearing loss, ID, midface hypoplasia, flat nose, depressed nasal bridge, hypertelorism, long philtrum, drooping mouth	AR	1 patient	Choucair et al., 2015
14	*SEC24D*	616294	4q26	Cole-Carpenter syndrome 2	Phenotype closely resembling Cole-Carpenter syndrome: severely disturbed ossification of the skull, multiple fractures with prenatal onset, short stature, macrocephaly, midface hypoplasia, micrognathia, frontal bossing, down-slanting palpebral fissures	AD	1 patient CSO	Garbes et al., 2015
15	*SHOC2*	602775	10q25.2	Noonan-like syndrome with loose anagen hair	Noonan-like syndrome: fetal hydrops, atrial tachycardia, fetal pleural effusion, short stature, developmental delay, macrocephaly, severe CSO	AD	1 patient CSO	Takenouchi et al., 2014
16	*SMC1A*	300040	Xp11.22	Cornelia de Lange syndrome	Craniofacial dysmorphisms, growth and developmental delay	XLD	1 patient CSO	Xu et al., 2018
17	*WDR19*	608151	4p14	Cranioectodermal dysplasia	Sensenbrenner/Jeune syndrome: nephronophthisis-like nephropathy, skeletal abnormalities (narrow rib cage, pectus excavatum, short limbs, brachydactyly), ectodermal defects, renal failure, hepatic fibrosis, heart defects, retinitis pigmentosa, sagittal suture synostosis	AR	1 patient CSO	Bredrup et al., 2011

I. **TERATOGENS***:* All environmental agents that produce structural alteration after fertilization are termed teratogens. Maternal exposure to these agents during the period of craniofacial organogenesis could result in malformations or disruptions. Teratogens include (a) prescription medications, associated metabolites and dietary supplements (b) recreational drugs; (c) toxins; and (d) hyperthermia.

II. **MATERNAL FACTORS***:* Lack of certain vitamins such as folic acid has been associated with a higher incidence of craniosynostosis. Alterations in maternal hormones are also thought to be correlated.

III. **INTRAUTERINE FACTORS***:* An abnormality in the intrauterine environment, such as fetal mandibular constraint due to multiple pregnancy or oligohydramnios, can cause sutural defect. Similarly, the presence of amniotic bands around the developing fetus can result in craniosynostosis due to disruption.[19]

SYNDROMES ASSOCIATED WITH CRANIOSYNOSTOSIS

The craniosynostoses are etiologically and pathogenetically heterogeneous. Premature sutural fusion may occur alone or together with other anomalies, making up various syndromes. Over **180** syndromes are known. Most cases of isolated craniosynostosis are sporadic, but familial instances are known. Familial lambdoid synostosis is rare. Associated anomalies are more frequent in coronal series than in sagittal series. The types of anomalies most commonly associated with syndromic craniosynostosis are limb defects, ear anomalies, and cardiovascular malformations.[20]

Syndrome	Essential Features	Inheritance
Apert, Apert-Crouzon	Craniosynostosis, severe syndactyly of hands and feet, down-turned mouth, hypertelorism	Autosomal dominant
Saethre-Chotzen	Craniosynostosis, facial asymmetry, low-hairline ptosis, deviated nasal septum, syndactyly of second and third fingers	Autosomal dominant
Pfeiffer, Noack	Craniosynostosis, malformed enlarged thumb and great toe, soft-tissue syndactyly of second and third digits, normal intelligence	Autosomal dominant
Crouzon, craniofacial dysostosis	Craniosynostosis, maxillary hypoplasia, shallow orbits with proptosis, bifid uvula or cleft palate	Autosomal dominant
Craniosynostosis, fibular aplasia, Lowry	Craniosynostosis and fibular aplasia	Autosomal recessive
Jackson-Weiss	Craniosynostosis with midface hypooplasia, mild syndactyly of feet, broad great toes	Autosomal dominant
Carpenter	Oxycephaly, mild syndactyly of fingers, preaxial polydactyly of feet, hypogenitalism, obesity, congenital heart disease	Autosomal recessive

Other miscellaneous syndromes associated with craniosynostosis are:

1) Acrocephalospondylosyndactyly
2) Acrocraniofacial dysostosis
3) Antley-bixler syndrome
4) Armendares syndrome
5) Baller-gerold syndrome
6) Beare-stevenson cutis gyrata syndrome
7) Berant syndrome
8) Cap syndrome
9) Calabro syndrome
10) Christian syndrome
11) Cranioectodermal dysplasia
12) Craniofrontonasal syndrome
13) Crouzonodermoskeletal syndrome
14) Curry-jones syndrome
15) Fontaine-farriaux syndrome

16) Gómez–lópez-hernández syndrome
17) Hall syndrome
18) Herrmann syndrome
19) Holoprosencephaly/craniosynostosis syndrome
20) Hypomandibular faciocranial syndrome
21) Jackson-weiss syndrome
22) Jones craniosynostosis/dandy-walker syndrome
23) Kozlowski craniosynostosis syndrome
24) Lowry-maclean syndrome
25) Meier-gorlin (ear-patella-short stature) syndrome
26) Sakati syndrome
27) Scarf syndrome
28) Ventruto syndrome
29) Wisconsin syndrome

CURRENT APPROACHES AND TREATMENT PHILOSOPHIES

Surgical treatment of craniosynostosis found its origins in the late 1800s, when techniques such as fragmentation of the cranial vault and linear craniectomy were employed. These early procedures were accompanied by a high rate of reossification and poor esthetic outcomes, mandating multiple subsequent procedures. Simple craniectomy, however, still finds limited use today for transient cranial decompression. These early procedures have now been supplanted by surgical remodeling of the affected area of the cranial vault and orbits. Surgery is generally performed at 6-9 months in order to take full advantage of the regenerative capacity of the skull at this age.[21]

Early attempts at surgical correction focused solely on removal of the pathologic suture by strip craniectomy. Refusion, however, invariably occurred, mitigating any gains made in the operating room.[22] More aggressive procedures have since evolved, encompassing remodeling of the entire calvarial vault in one sitting. Such procedures separate both the bifrontal and biparieto-occipital fragments to allow for recontouring using radial osteotomies, followed by wire or suture fixation back to a shortened midline parietal segment. Each parietal bone is also removed and remodeled to increase lateral convexity prior to reattachment with the underlying dura mater alone. This approach not only releases the synostotic constraint, but also augments transverse width and improves calvarial contour.[23] Finally, as an alternative, less invasive strategy, endoscopic extended strip craniectomy in conjunction with postoperative molding helmet therapy has recently been utilized for the correction of sagittal synostosis.[24]

Considering the extensive nature of procedures aimed at remodeling the calvarial vault, complications can occur following surgical therapy for craniosynostosis. While many studies have reported a mortality rate as high as 2.3%, most international figures fall in the range of 1.5–2%.[24] Most deaths were attributed to hemorrhagic complications, but a variety of other causes have also been reported including air emboli, cerebral edema and respiratory infections. Like hemorrhage, infection is another significant concern following calvarial remodeling.

Resultant swelling, erythema, tenderness or purulent drainage may be noted postoperatively. Lastly, neurologic complications, including cerebrospinal fluid leak and seizures secondary to intracerebral contusion/bleeding, are salient considerations which must be recognized to conclude, At the time of infancy and childhood, the calvaria expands to accomadate the growing brain. This expansion occurs at the narrow seams of undifferentiated mesenchyme, called as cranial sutures, which lie between different bones.[23]

CONCLUSION

C**raniosynostosis** describes the premature fusion of one or more of the cranial sutures leading to secondary distortion of skull shape because of a combination of lack of growth perpendicular to the fused suture and compensatory overgrowth at the non-fused sutures. The overall prevalence of craniosynostosis has been estimated at between 1 in 2100 and 1 in 2500 births.

Craniosynostosis can be divided into isolated or syndromic type and non-syndromic type. In the majority of cases, the disease is isolated and nonsyndromic and, in more severe cases, it might be complicated with increased intracranial pressure, visual impairment, hearing loss, sleep disturbances, choanal atresia, or psychomotor delay with intellectual disability. In syndromic craniosynostoses, the skull deformity is associated with additional clinical symptoms that may include hand and feet malformations, skeletal and cardiac defects, developmental delay and others.

Left untreated, craniosynostosis can result in worsened cranial deformity and, potentially, overall cranial growth restriction with resultant increased ICP. The deformity may lead to psychosocial issues as the child interacts with peers during development.

Because of the risks associated with untreated craniosynostosis, it is usually treated surgically soon after diagnosis. There are two steps in the management of the case of craniosynostosis; acute and elective management. In acute management care of neonates and infants with severe multisuture synostosis is done which is directed towards maintenance of the airway, support of feeding, eye protection and treatment of raised ICP. To unlock and reshape the bones elective management is done. It has three major objectives, which are to correct the skull deformity, prevent its progression and reduce the future risk of raised ICP.

Regular follow-up throughout childhood is advisable, particularly to monitor for symptoms of raised ICP, such as headaches, behaviour change, or decline in school performance.

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