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Review

Fibroblast Growth Factor Receptor 2 (*FGFR2*) Mutation Related Syndromic Craniosynostosis

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Abstract

Craniosynostosis results from the premature fusion of cranial sutures, with an incidence of 1 in 2,100-2,500 live births. The majority of cases are non-syndromic and involve single suture fusion, whereas syndromic cases often involve complex multiple suture fusion. The fibroblast growth factor receptor 2 (*FGFR2*) gene is perhaps the most extensively studied gene that is mutated in various craniosynostotic syndromes including Crouzon, Apert, Pfeiffer, Antley-Bixler, Beare-Stevenson cutis gyrata, Jackson-Weiss, Bent Bone Dysplasia, and Seathre-Chotzen-like syndromes. The majority of these mutations are missense mutations that result in constitutive activation of the receptor and downstream molecular pathways. Treatment involves a multidisciplinary approach with ultimate surgical fixation of the cranial deformity to prevent further sequelae. Understanding the molecular mechanisms has allowed for the investigation of different therapeutic agents that can potentially be used to prevent the disorders. Further research efforts are need to better understand screening and effective methods of early intervention and prevention. Herein, the authors provide a comprehensive update on *FGFR2*-related syndromic craniosynostosis.

Key words: Fibroblast Growth Factor Receptor; Mutations, Syndromic; Craniosynostosis.

Introduction

Craniosynostosis results from the premature fusion of cranial sutures, with an incidence of 1 in 2,100-2,500 live births (1–4). In normal development, cranial growth occurs perpendicular to suture lines leading to a well-proportioned head with a longer anteroposterior than bitemporal dimension (5). Sutures typically fuse in an orderly fashion with the first suture – metopic – closing within the first year of life and the final sutures squamosal and lambdoidal not closing until the fourth or fifth decade of life. Premature fusion of one or more sutures precludes growth of cranial bones perpendicular to the affected sutures and leads to compensatory growth in a parallel direction, resulting in a cranial dysmorphic head shape (6,7).

The vast majority of craniosynostoses involve single suture fusion, though multiple sutures can be affected (5). Depending on which sutures prematurely fused, patients will have characteristic phenotypes. There are four major sutures including sagittal, coronal, metopic and labdoid, as well as minor sutures including frontonasal, temporosquamosal, and frontosphenoidal. The sagittal suture is involved in 40-58% of cases, followed by unilateral or bilateral coronal (20-30%), metopic (5-15%) and lambdoid (2-4% of cases) suture fusion (3, 5, 8). Sagittal suture fusion results in an increase of the anterior-posterior diameter resulting in dolichocephaly or

scaphocephaly (5). Unilateral coronal synostosis results in anterior plagiocephaly whereas bilateral coronal fusion results in brachycephaly. Premature metopic suture fusion is associated with triangular shaped forehead, trigonocephaly. Lambdoid synostosis is usually unilateral, resulting in asymmetric posterior plagiocephaly, whereas bilateral lambdoid synostosis results in flattened and widened occipital region (5). Kleeblattschadel or cloverleaf skull is a term given for a trilobed skull resulting from synostosis of lambdoidal and coronal sutures.

Cases of craniosynostoses are thought to result from a complex interaction of environment, epigenetics, and genetics (9, 10). Evidence from a population-based study suggests that multiple births, maternal age greater than 35, birth weight >4000 g, and male sex are risk factors for craniosynostosis (11). Other potential risk factors include advanced paternal age, higher parental education, maternal exposure to valproate acid, preterm delivery, and in-utero growth constraint (1,12–14). The vast majority of these cases are non-syndromic and 80-90% of cases involve a single suture line (15). On the contrary, approximately 10-20% of craniosynostosis cases are syndromic, mostly with autosomal dominant inheritance, incomplete penetrance, and variable expressivity (6). The syndromic synostoses, such as Crouzon, Apert, and Pfeiffer, may involve multiple sutures and extracranial phenotypes are mostly of the hands and feet (16). Occasionally complex or multisuture craniosynostosis occurs in patients without an identifiable syndrome (17). Although there have been reports of prenatal diagnoses of craniosynostosis, the majority are diagnosed postnatally including those associated with syndromes.

Recently, whole exome and genome sequencing has enabled identification of hundreds of mutations implicated in craniosynostosis. Genes most commonly mutated in familial craniosynostosis include *FGFR*2, *FGFR3*, twist homologue 1 (*TWIST1*) and ephrin-B1 (*EFNB1*) (2,18–21) Of these, FGFR variants have been most extensively characterized and serve as a basis for understanding the molecular underpinnings of craniosynostosis. Herein, the authors provide a comprehensive update on *FGFR2*-related syndromic craniosynostosis.

Fibroblast growth factor (FGF) receptors (FGFRs)

The FGF family, comprised of at least 22 known FGF ligands, binds to five related receptor tyrosine kinases, resulting in receptor monomer dimerization, activation of kinase domains and phosphorylation of the receptor (22–24). It is well known that FGF/FGFR signaling plays important roles in numerous biological processes, including bone development and homeostasis by controlling differentiation of mesenchymal and neuroectoermal cells (25–27). Mutations in three members of the FGFR family (*FGFR1*, *FGFR2*, and *FGFR3*) result in unregulated FGF signaling and premature suture closure. Much of the current knowledge regarding the role of FGF/FGFR in cranial growth is derived from mouse models. With the exception of *FGFR5*, members of the FGFR gene family encode a receptor tyrosine kinase (RTK), which has an extracellular ligand-binding portion composed of immunoglobulin-like domains (IgI, IgII, and IgIII), a transmembrane region, and intracellular tyrosine kinase domains (TK1 and TK2) (Figure 1) (3, 28–32).

Within the IgII domain, a positively charged conserved region serves as the binding site for heparin sulphate (26). FGF binding occurs at IgII and IgIII as well as the link between these Ig-like domains. Alternative splicing in the IgIII domain results in various isoforms of the receptor with differing affinities for FGF ligands. The N-terminal part of the IgIII domain is encoded by exon IIIa and the C-terminal part is encoded by either exon IIIb or IIIc (26).

Ligand binding activates downstream pathways including phosphoinositide 3-kinase (PI3K)/Akt, protein kinase C, phospholipase C, and mitogen-activated protein kinase [20, 27, 28]. Downstream of RAS, the extracellular signal-related kinases 1 and 2 (ERK1/2) are key proteins mediating mitogen-activated protein kinase (MAPK) in FGFR2 signaling (31,33). Recent evidence suggests that reduced levels of ERF, which encodes an inhibitory ETS transcription factor directly bound to ERK1/2, results in complex multisuture craniosynostosis in humans and mice (32,34). This suggests that FGFR2 mediated ERK-MAPK activity regulates coronal suture formation (34).

Craniosynostotic disorders caused by mutations in *FGFR2* gene are perhaps the most extensively studied (35). Both minor and major sutures fusion occurs in most patients with *FGFR2*-related craniofacial dyostosis (36). Abundant FGFR2 expression is found in the cartilage of the cranial base (25,37–39). FGFR2 in cranial sutures is largely expressed in differentiating osteoblasts and osteoprogenitor cells. Via downstream pathways, FGF/FGFR2 signaling mediates osteoprogenitor proliferation, differentiation, and apoptosis (25,40). Early differentiation is thought to be a leading factor involved in premature suture fusion (3). As will be discussed, autosomal dominant *FGFR2* mutations enhance receptor signaling through dimerization independent of ligand binding with resultant

constitutive activation (41,42). Most pathogenic variants of *FGFR2* are missense variants, with less frequent reports of deletions, insertions, and splice site mutations (28). Mutations in *FGFR2* less commonly result in non-syndromic craniosynostoses. The discussion in this review will be limited to *FGFR2*-related syndromic craniosynostosis.

FGFR2-related syndromic craniosynostosis

Heterozygous activating mutations of *FGFR2* result in several craniosynostosis syndromes, such as Crouzon, Apert, Pfeiffer, Antley-Bixler, Beare-Stevenson cutis gyrata, Jackson-Weiss, Bent Bone Dysplasia, and Seathre-Chotzen-like syndromes (43–47) (Table 1). Whereas the majority of mutations in *FGFR2* localize to two exons encoding the extracellular IgIII domain (IIIa/exon 8, and IIIc/exon 10), mutations have been identified in exons coding the tyrosine kinase region (exons 3, 5, 14, 15, 16 and 17), and exon 11 that encodes the transmembrane domain, as well as the IgI and IgII domains (48–51) (Table 1).

Both Crouzon and Pfieffer are typically inherited in an autosomal dominant fashion and have similar molecular mechanisms. Crouzon is usually the mildest of the syndromes. Bicoronal synostosis is most common in Crouzon syndrome; however, pansynostosis may also be a late presenting feature in some cases. The crouzonoid facial appearance, which consists of flattened forehead, proptosis, hypertelorism, beaked nose, and midface hypoplasia without major limb deformities characterizes the disorder (26, 52) (Table 1).

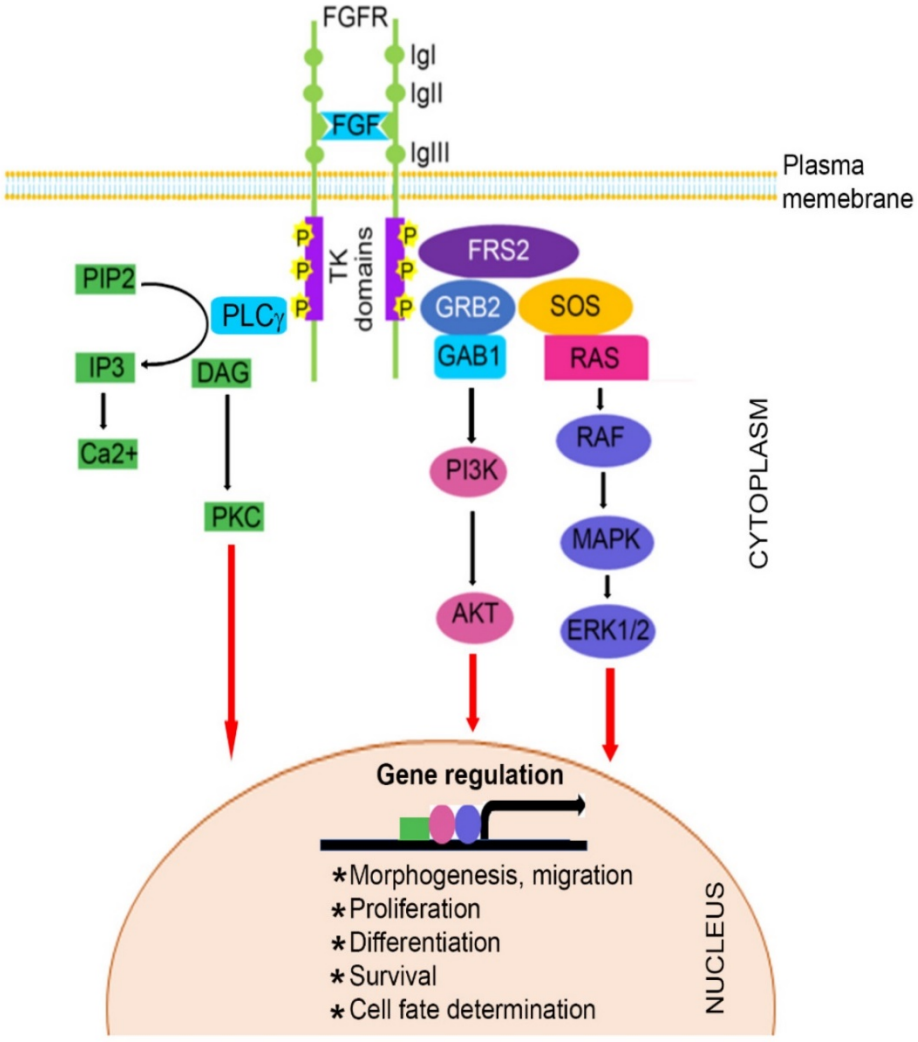

Figure 1. Schematic representation of FGFR signaling pathway. A typical FGFR gene encodes a tyrosine kinase (TK) receptor. This receptor has an extracellular ligand-binding sites, which are comprised of immunoglobulin-like domains (IgI, IgII and IgIII), transmembrane region and divided intracellular tyrosine kinase domains, TK1 and TK2. The signaling pathway mainly operates through at least 3 distinct pathways. Initiation of RAS/MAPK pathways starts with formation of FRS2 complex and regulates cell proliferation and differentiation. The PI3K/AKT pathway controls cells survival and fate determination after getting initiated by FRS2 complex formation. Activation of PKC pathway started with binding of PLCγ to the activated FGFR and regulates morphogenesis and migration of cells.

Table 1. FGFR2- Associated Craniosynostotic Syndromes

Syndrome	Inheritance	Mutations	Craniosynostosis Findings	Extracranial Phenotypes	Ref.
Crouzon Syndrome	Autosomal dominant	Cys278Phe, Trp289Gly, Tyr290Gly, Ser267Pro, Tyr328Cys, Gly338Arg, Tyr340His, Cys342Tyr, Cys342Arg, Cys342Phe, Cys342Ser, Cys342Trp, Ala344Gly, Asn549Thr, Ser347Cys, Ser354Cys	Bicoronal synostosis, pansynostosis late	Crouzonoid face (flattened forehead, proptosis, hypertelorism, beaked nose, midface hypoplasia), normal hands	[35, 51,54-56,61]
Pfeiffer Syndrome	Autosomal dominant	Ala314Ser, Asp321Ala, Thr342Pro, Cys278Phe, Cys342Tyr, Trp290Cys, Tyr340Cys, Cys342Tyr, Cys342Arg, Cys342Ser, Cys342Trp, Ser351Arg, Val359Phe	Type I: Bicoronal synostosis Type II: Kleeblattschädel (cloverleaf skull) and extreme proptosis Type III: Bicoronal synostosis, No cloverleaf skull	Nasal abnormalities, proptosis, hypertelorism, frontal bossing, broad thumbs and great toes, hydrocephalus with type II	[35,52, 55-57,61, 104]
Apert Syndrome	Autosomal dominant	Ser252Trp, Pro253Arg, Ser252Phe	Bicoronal synostosis	Midface hypoplasia, macrocephaly, downslated palpebral fissues, radial deviation of thumb, severe syndactyly of hands and feet	[3, 63-65]
Antley-Bixler Syndrome	Autosomal recessive/ dominant forms	Ser351Cys Tyr290Cys	Multisuture synostosis	Midface hypoplasia, radiohumeral synostosis, joint contractures and arachnodactyly	[77-82]
Beare-Stevenson cutis gyrata syndrome	Autosomal dominant	Tyr375Cys, Ser372Cys	Kleeblattschädel deformity	Cutis gyrata (furrowed skin), ear defects, anogenital deformities	[83-94]
Jackson-Weiss Syndrome	Autosomal dominant	Ala344Gly, Glu289Pro, Ser347Cys, Cys342Arg, Cys342Ser	Variable	Facial dysmorphism and foot malformations (hands typically normal)	[10, 35, 95-99]
Bent Bone Dysplasia syndrome	Autosomal dominant	Tyr381Asp, Met391Arg	Bicoronal synostosis	Dysmorphic oral maxillofacial features as well as hypoplastic pubis, clavicles, osteopenia, and bent long bones	[40, 99,100]
Seathre-Chotzen-like syndrome	Autosomal dominant	Gln289Pro VV269-70del	Heterogeneous patterns of craniosynostosis: uni- or bicoronal, sagittal, or metopic synostosis	Syndactyly of hands and feet, ptosis, hearing loss, hypertelorism, and spine abnormalities	[35,101-103]

The flattened forehead is secondary to bicoronal synostosis. In Pfieffer syndrome, the craniofacial severity is variable and extracranial manifestations include big toes and broad radially deviated thumbs (53). Various clinical subtypes of Pfieffer syndrome have been described, type 1 being compatible with life, and types 2 and 3 associated with more severe complex synostosis and higher associated mortality (54). The craniofacial features of the Pfieffer syndromes differ somewhat: type 1 typically has moderate-to-severe midface hypoplasia, type 2 has cloverleaf skull and extreme proptosis, and type 3 is characterized by turribrachycephaly (a high and prominent forehead) as well as proptosis (28). The *FGFR2* mutations in Crouzon and Pfeiffer syndrome overlap, most often occurring in extracellular IgIII domain encoded by exons 8 (IIIa) or 10 (IIIc) (46). Both syndromes may be caused by the Cys278Phe and Cys342Tyr missense mutations (55–57). Severe cases of Pfeiffer syndrome are caused by a small subset of substitutions encoding Trp290Cys, Tyr340Cys, Cys342Arg or Ser351Cys (58–60). The Trp290Cys mutation has also been linked to tracheal cartilaginous sleeves in children with syndromic craniosynostosis (61). Recently, Ke and colleagues presented a unique report on a young boy with Crouzon syndrome who had bicoronal craniosynostosis, proptosis, and maxillary hypoplasia and identified a heterozygous Ser267Pro mutation in exon 8 (55). Other mutations identified in patients with features resembling the Crouzon/Pfeiffer syndrome include Leu617Phe mutation in the TK domain and Gly271Val in the IgIIIa domain of *FGFR2* (62). A unique mutation leading to Ala315Ser in FGFR2 has also been identified in in a family with a mild phenotype of Crouzon craniofacial dyostosis but without overt craniosynostosis (63). A report from Japan also identified a novel *FGFR2* Asn549Thr mutation in a patient with Crouzon syndrome (10).

Apert syndrome is characterized by bicoronal synostosis, midface hypoplasia, and complex syndactyly involving both hands and feet (Table 1). The abnormal skull morphology is a result of maldevelopment of brain calvarias and cranial base (64). This fusion of the digits differentiates Apert syndrome from other *FGFR2*–related syndromes. Apert syndrome mutations have been shown to follow autosomal dominant inheritance (3,65,66). Apert syndrome is typically caused by specific missense mutations of the highly-conserved linker region between IgII and IgIII domains of *FGFR2*, most often either Ser252Trp or Pro253Arg (16,43,67–69). Cleft palate can also occur in this disorder, most commonly in those with Ser252Trp mutations (43). Other studies corroborate the findings of Ser252Trp and Pro253Arg mutations in majority of patients with

FGFR2 related Apert syndrome, although Ser252Trp variant is more common, and Ser252Phe mutations have also been reported (44,70–72). Interestingly, unlike the Ser252Trp variant, the Pro253Arg mutation results in generalized increased affinity of FGFs to FGFR2 (28,73). Such receptor mutations exhibit selective decrease in the dissociation kinetics of FGF2 but not of other FGF ligands examined (74). Recently, Andreou and colleagues reported a young girl with Pro253Arg *FGFR2* mutation-associated Apert syndrome who also had early-onset low-grade papillary carcinoma (75). Studies by Lomri et al. on Apert syndrome provided evidence to suggest that *FGFR2* mutations resulted in greater numbers of precursor cells entering the osteogenic pathway, which lead to premature calvarial ossification and bone matrix formation (76). *FGFR2* mutations may result in premature suture fusion through upregulation of epidermal growth factor (EGF) and platelet derived growth factor (PDGF) α signaling (77).

Antley-Bixler is a rare syndrome associated with multisuture synostosis as well as a broad spectrum of other congenital anomalies including midface hypoplasia, radiohumeral synostosis, joint contractures and arachnodactyly (Table 1) (78–80). Prognosis is poor and mortality in the newborn is high, largely from airway issues. Although the syndrome has been described for several decades now, the molecular basis is evolving (81). Antley-Bixler syndrome was thought to have autosomal recessive inheritance, but more recently evidence has emerged of a dominant *de novo* mutation in *FGFR2* resulting in a Ser351Cys amino acid substitution in the IgIII domain (82,83). These findings suggest that there may be both an autosomal recessive and dominant form.

Beare-Stevenson cutis gyrata syndrome is characterized by several anomalies in addition to the skin condition of redundant and convoluted folds, including craniosynostosis, ear defects, anogenital anomalies (Table 1) (84–86). The syndrome follows an autosomal dominant inheritance pattern. Although the syndrome is exceedingly rare with only a few cases reported, the majority of the patients with craniosynostosis had severe Kleeblattschadel deformity (87–90). Beare-Stevenson is caused by *de novo* heterozygous mutations in *FGFR2*, including Tyr375Cys mutation in the transmembrane domain, and Ser372Cys mutation in the carboxy-terminal end of the linker region between IgIII and transmembrane domains (90–94). These activating point mutations account for the majority of Beare-Stevenson syndrome cases. A *de novo* heterozygous 63-bp deletion in the *FGFR2* was also noted in a boy presenting with Beare-Stevenson, and the authors proposed that such a deletion would alter the splicing of isoform IIIc (95). However, in the same report, no mutations were found in a few patients with the syndrome, suggesting genetic heterogeneity.

Jackson-Weiss syndrome is another rare craniosynostostic disorder, with variable phenotypes, inherited in an autosomal dominant fashion (Table 1). Patients with this syndrome also demonstrate facial dysmorphism and foot malformations including tarsal/metatarsal fusion, although the hands are normal in appearance (96). Further investigation of one of the families described in the original report of Amish kindreds led to the identification of Ala344Gly mutation in the conserved region of IgIII domain of *FGFR2* (97). Similarly, other reports have confirmed missense mutations in *FGFR2* exons IIIa and IIIc in Jackson-Weiss, including a Glu289Pro mutation in exon IIIa (98,99). A novel *FGFR2* Ser347Cys mutation was identified in a Japanese patient with Jackson-Weiss syndrome (10).

De novo FGFR2 mutations have been identified in Bent Bone Dysplasia (BBDS), a rare occurring perinatal lethal skeletal dysplasia of autosomal dominant inheritance. BBDS is characterized by craniosynostosis, dysmorphic oral maxillofacial features as well as hypoplastic pubis, clavicles, osteopenia, and bent long bones (100,101). One study demonstrated that four individuals affected with this disorder were heterozygous for missense mutations that resulted in the addition of a polar amino acid to the hydrophobic transmembrane region of the receptor (100). In BBDS, unique mutations reduce receptor levels at the plasma membrane and decrease responsiveness to FGF2, therefore attenuating canonical signaling. Heterozygosity for the *de novo* missense mutations Tyr381Asp and Met391Arg has been reported (100). More recently, in addition to canonical signaling at the plasma membrane, FGFR2 has been shown to regulate bone formation within the nucleolus (40). These aforementioned mutations also enhance nucleolar occupancy of FGFR2 at the ribosomal DNA (rDNA) promoter (40).

Seathre-Chotzen is yet another autosomal dominant craniosynostotic condition most commonly associated with mutations in the *TWIST* gene (Table 1). However, Paznekas and colleagues reported on a single case with a val-val deletion in FGFR2 (102). Several years later, a Gln289Pro mutation in *FGFR2* was detected in a family with Saethre-Chotzen syndrome (103). The spectrum of craniosynostosis observed may be either uni- or bicoronal, with sagittal suture fusion exceedingly rare and metopic suture fusion found in few reports (104). Other features of the disorder include short stature, including

syndactyly of hands and feet, hypertelorism, ptosis, and abnormalities of the spine.

An unspecified craniosynostosis syndrome, craniofacial-skeletal-dermatological dysplasia, has been associated with a Trp290Cys mutation in the extracellular domain of *FGFR2* (105). This syndrome is characterized by complex multiple suture craniosynostosis, hydrocephalus, corneal scleralization, atresia of auditory meatus, choanal stenosis, broad thumbs and great toes, scoliosis, acanthosis nigricans, and mental retardation.

Syndrome management

Management of syndromic craniosynostosis is optimized by a multidisciplinary approach involving plastic and reconstructive surgeons, neurosurgeons, neurologists, pediatricians, and genetic counselors. Various imaging modalities are used to better facilitate prenatal diagnosis including ultrasound, magnetic resonance imaging (MRI) and genetic testing (106). Ultrasound may be used to look for associated limb anomalies and craniofacial dysmorphologies that may point to a particular syndrome. 3-D ultrasound and MRI should be used to further assess findings suspicious for a craniosynostosis syndrome on two-dimensional ultrasound (53,107). MRI is particularly helpful in evaluating associated central nervous system anomalies.

Given the autosomal dominant inheritance pattern of *FGFR2*-related craniosynostosis syndromes, genetic counseling is critical once the diagnosis is confirmed. Follow-up should be scheduled regularly to monitor for signs and symptoms of increased intracranial pressure. Once a pathogenic variant has been identified, prenatal testing is possible, although the predictive value is poor. Non-invasive means such as the use of cell-free fetal DNA present in the maternal blood to assess for known pathogenic gene mutations is possible in the first trimester (108). Amniocentesis and chorionic villus sampling are invasive procedures traditionally use for prenatal screening. Testing for pathogenic variants of genes such as FGFR2 is indicated in high-risk pregnancies with family histories significant for craniosynostosis, but routine fetal ultrasound is sufficient for low-risk pregnancies (106).

Treatment is typically geared towards surgical correction of the clinical manifestations, the prevention of future deformation, while reducing the risk of increased intracranial pressure. Surgery is done emergently in cases of increased intracranial pressure. Otherwise, the optimal timing for fixation remains controversial, with some surgeons preferring early intervention to allow for expansion of a constricted brain and corneal protection, and others delaying surgery to allow for more stability of the skull in order to decrease the need for revisional surgery (106). The goal of surgery is to improve skull, orbit, and facial deformities. Whereas experience has shown that single suture craniosynostosis can often be managed successfully with a single surgical procedure, complex/multiple suture craniosynostosis often necessitates a staged approach (17). Surgical correction methods include open calvarial reconstruction, distraction, and less invasive techniques such as regional cranioectomy, liberation of occipital bone flap and spring-mediated cranial vault remodeling (106,109). Increasing experience at the Children's Hospital of Philadelphia, a high-volume center for syndromic craniosynostosis surgery, has favored posterior cranial vault distraction over fronto-orbital advancement as the initial cranial remodeling procedure (106). Posterior cranial vault distraction has several advantages including superior cranial volume expansion, improvements in anterior and posterior cranial morphology, with favorable morbidity profile (106). Early data in patients with Apert syndrome suggests that the overall number of major craniofacial procedures within the first 5 years of life is decreased following early posterior cranial vault distraction (106).

Pharmacologic blockade of craniosynostotic pathways

There is a developing interest in inhibiting the molecular pathways involved in the development of craniosynostosis in the aforementioned syndromes. A soluble form of *FGFR2* with Ser252Trp mutation inhibits osteoblastic differentiation caused by gain-of-function mutations in *FGFR2* in an Apert mouse model, and partially prevents craniosynostosis (110–112). Further attenuation of the signaling pathways has also been shown to prevent premature suture fusion (113). Uncoupling of the docking protein FRS2 and activated FGFR2 (Figure 1) leads to normal skull development in a murine model of Crouzon-like craniosynostosis (113). Using a murine model, Xu and colleagues showed that an activating mutation in *FGFR2* results in increased trabecular bone formation and decreased bone resorption through a Wnt/β-catenin-dependent anabolic effect (114). Pharmacologic inhibition of Wnt/β-catenin signaling partially reverses this process (114). These early studies provide support for developing agents that inhibit the pathways that lead to craniosynostosis. Also, knowing that patients previously diagnosed with *FGFR2*-related Crouzon syndrome had ERF-related craniosynostosis, ERF may

serve as an target for therapeutic modulation (32,115). In a mouse model of craniosynostosis, Shukla and colleagues demonstrated that a small hairpin RNA targeting the dominant mutant form of *FGFR2* prevents craniosynostosis in mice (116,117). Pharmacologic blockade of mitogen-activated protein (MAP) kinase 1 and 2 (MEK1/2)/ERK pathway (Figure 1) by U0126 in mutant mice significantly inhibits craniosynostosis (116). These authors proposed that small-molecules could potentially be used for both prevention and therapy.

Compared to the investigations underway for *FGFR*-related malignancies, less progress has been made with regard to therapeutic strategies for *FGFR*-related skeletal and craniosynostotic disorders. Tyrosine kinase inhibition is one such promising strategy in mutated *FGFR*-related craniosynostotic conditions (118). PD173074, an FGFR tyrosine kinase inhibitor, has been used in a model of *FGFR2* related Crouzon syndrome, demonstrating coronal suture patency and no evidence of craniosynostosis (119). Wang et al. observed ligand-independent phosphorylation of FGFR2 in a model of Beare-Stevenson cutis gyrate syndrome and p38 MAPK pathway activation (120). The use of p38 kinase inhibitor suppressed premature suture closure in mutated mice (120). Recently, a tyrosine kinase inhibitor (Figure 1), ARQ 087, has been shown to rescue the major pathological effects of activating mutations in *FGFR1, FGFR2,* and *FGFR3* in experimental models of chondrodysplasias and craniosynostosis (121).

Conclusions and future aspects

The *FGFR2* is perhaps the most extensively studied gene that is mutated in various craniosynostotic syndromes including Crouzon, Apert, Pfeiffer, Antley-Bixler, Beare-Stevenson cutis gyrata, Jackson-Weiss, Bent Bone Dysplasia, and Seathre-Chotzen-like syndromes. The majority of these mutations are missense mutations that result in constitutive activation of the receptor and downstream molecular pathways. Treatment involves a multidisciplinary approach with ultimate surgical fixation of the cranial deformity to prevent further sequelae. Understanding the molecular mechanisms has allowed for the investigation of different therapeutic agents that can potentially be used to prevent the disorders. Genetic studies are recommended for not only individuals with known syndromic features, but also for family members with uncommon or normal phenotypes to improve counseling outreach.

One of the more fascinating questions in the biology of the *FGFR2* gene is why mutations in this single gene can give rise to such a wide range of disorders with such a broad spectrum of phenotypes. As seen in the preceding sections, some disorders involve single suture synostosis, whereas others affect multiple sutures. Some disorders are principally confined to the craniofacial skeleton, whereas others have prominent extracranial dysmorphologies. Given the extensive study of *FGFR2* mutations in clinical samples, this gene could prove an interesting test case for systematically mapping genotype-phenotype relationships in a highly conserved pathway. It will be interesting to discover whether various mutations in *FGFR2* and its pathway members have subtly different activities, and how these activities give rise to the observed spectrum of phenotypes. Another possibility is that modifier genes alter the phenotypic response in patients to a common array of gain or loss of function mutations. The accumulation of patient sequencing data and more studies in animal models will be important to sorting out these possibilities.

Further research efforts are need to better understand screening and effective methods of early intervention and prevention. Also, knowing that some individuals with mutations may be phenotypically normal and have syndromic offspring, a better understanding of the genetic, epigenetic, and environment interplay is critical. When deciding surgical options for patients with craniosynostosis, more data is necessary to guide optimal timing of intervention as well as the best method of cranial remodeling to allow for minimal morbidity and less need for future interventions.

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Competing Interests

The authors have declared that no competing interest exists.

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