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Genetic Causes of Craniosynostosis: An Update

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Abstract
In 1993, Jabs et al. were the first to describe a genetic origin of craniosynostosis. Since this discovery, the genetic causes of the most common syndromes have been described. In 2015, a total of 57 human genes were reported for which there had been evidence that mutations were causally related to craniosynostosis. Facilitated by rapid technological developments, many others have been identified since then. Reviewing the literature, we characterize the most common craniosynostosis syndromes followed by a description of the novel causes that were identified between January 2015 and December 2017.

Craniosynostosis occurs in 1:2,100–2,500 live births [Lajeunie et al., 1995a; Boulet et al., 2008; Miller et al., 2017], and the prevalence is reported to be rising [Cornelissen et al., 2016]. It is characterized by the premature fusion of calvarial sutures. This fusion restricts the normal growth of the skull, brain, and face (see Fig. 1). Therefore, surgical correction is often needed within the first year of life [Utria et al., 2015]. Craniosynostosis can be isolated, without any additional anomalies, or as part of a syndrome, often caused by a genetic alteration. A detectable genetic cause is more likely if coronal suture or multiple suture synostosis is observed, if a patient shows symptoms of growth or developmental retardation, and/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 [Timberlake and Persing, 2018].

In 1993, Jabs et al. were the first to describe a genetic origin of syndromic craniosynostosis. They identified a mutation located in the *MSX2* gene in a patient with Boston type craniosynostosis [Jabs et al., 1993]. Since this discovery, the genetic causes of the most common syndromes have been described [Passos-Bueno et al., 2008]. Mutations have been identified in the fibroblast growth factor receptor 2 (*FGFR2*) for Apert [Wilkie et al., 1995; Oldridge et al., 1999], Crouzon [Reardon et al., 1994], Pfeiffer [Muenke et al., 1994; Robin et al., 1994], Jackson-Weiss [Cohen, 2001], and Beare-Stevenson cutis gyrata syndrome [Przylepa et al., 1996] as well as for bent bone dysplasia [Merrill et al., 2012]. Mutations have been identified

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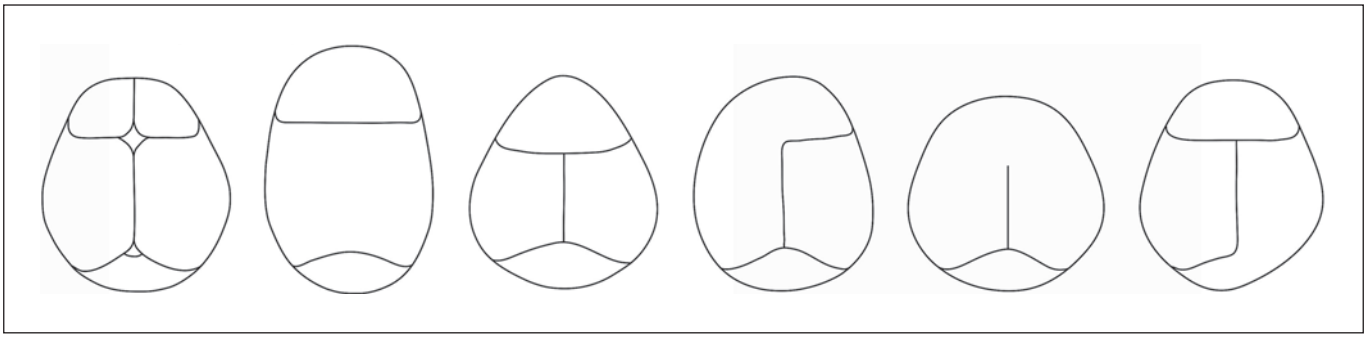

Fig. 1. Craniosynostosis. From left to right: normal calvarial sutures, sagittal suture synostosis leading to a scaphocephalic head shape, metopic suture synostosis leading to trigonocephaly, left coronal suture synostosis leading to left-sided plagiocephaly, bicoronal suture synostosis leading to a brachycephalic head shape, and right lambdoid suture synostosis leading to right-sided occipital plagiocephaly.

in *FGFR3* for Muenke syndrome [Bellus et al., 1996; Moloney et al., 1997; Muenke et al., 1997] and Crouzon syndrome with acanthosis nigricans [Meyers et al., 1995], in *TWIST1* for Saethre-Chotzen syndrome [Howard et al., 1997], in *ERF* for *ERF*-related craniosynostosis [Twigg et al., 2013b], in *TCF12* for *TCF12*-related craniosynostosis [Sharma et al., 2013], and in *EFNB1* for craniofrontonasal syndrome (CFNS) [Wieland et al., 2002, 2004; Twigg et al., 2006, 2013a] (in the order of frequency) [Sharma et al., 2013]. Besides these single-gene origins, another large group is caused by chromosomal rearrangements (approximately 13%) [Wilkie et al., 2010; Sharma et al., 2013].

In 2015, a total of 57 human genes were described for which there had been evidence that mutations were causally related to craniosynostosis (based on at least 2 affected individuals with congruent phenotypes). These genes can be divided into 2 broad groups. First, a group of 20 genes causing syndromes that are frequently associated with craniosynostosis (>50%; core genes). Second, a group of genes that cause disorders that are probably causally associated with craniosynostosis but only in a minority of the cases [Twigg and Wilkie, 2015]. Since the publication of this gene list, facilitated by rapid technological developments, another 22 genes have been identified since then. In the following, we describe the most common craniosynostosis syndromes and the newly identified causes.

Fibroblast Growth Factor Receptors

All fibroblast growth factor receptors originate from the same ancestral gene [Johnson and Williams, 1993]. They code for a group of transmembrane-receptor tyrosine kinases crucial for early embryonic development. FGFR1, FGFR2, and FGFR3 comprise the same structure with 3 extracellular immunoglobulin-like domains (IgI, IgII, and IgIII), a single-pass transmembrane segment, and a split tyrosine kinase (TK1/TK2) domain [Jaye et al., 1992; Johnson and Williams, 1993; Kan et al., 2002]. Identical proline to arginine mutations are seen in *FGFR1*, *FGFR2*, and *FGFR3*, pointing to a common pathogenesis [Bellus et al., 1996].

FGFR2 and *FGFR3* are subject to the paternal age effect; that is the introduction of mutations in *FGFR2* and *FGFR3* [Goriely and Wilkie, 2010], and in other genes involved in growth-factor receptor-RAS signaling such as *RET*, *PTPN11*, and *HRAS* [Goriely et al., 2009; Goriely and Wilkie, 2010; Schubbert et al., 2007] are characterized as gain-of-function mutations with near-exclusive paternal origin, high apparent germline mutation rate (up to 1,000-fold above background), and elevated paternal age (by 2–5 years, compared to the population average) [Goriely and Wilkie, 2010]. These mutations are positively selected and expand clonally in normal testes, leading to relative enrichment of mutant sperm over time (a process known as selfish spermatogonial selection) [Goriely and Wilkie, 2012].

FGFR2

FGFR2 maps to chromosome 10q25.3q26. Alternative splicing of *FGFR2* leads to many isoforms including keratinocyte growth factor receptor and bacterially expressed kinase [Twigg et al., 1998] which have different ligand specificities [Dell and Williams, 1992; Miki et al., 1992; Gilbert et al., 1993; Ornitz et al., 1996; Del Gatto et al., 1997; Carstens et al., 1998; Xu et al., 1998] as cited in Oldridge et al. [1999].

Specific missense mutations in *FGFR2*, p.(Ser252Trp) and p.(Pro253Arg), can lead to the autosomal dominant Apert syndrome (OMIM 101200) [Wilkie et al., 1995]. Also *Alu*-element insertions in *FGFR2* were identified to cause the syndrome [Oldridge et al., 1999]. It is hypothesized that Apert syndrome is explained by gain-of-function mutations that lead to increased affinity of mutant receptors for specific FGF ligands [Anderson et al., 1998]. Reproductive fitness is low, and more than 98% of the cases arise de novo. Apert syndrome is characterized by bicoronal synostosis and severe symmetrical syndactyly of the hands and feet. Other malformations occur, such as cleft soft palate or bifid uvula, fusion of the cervical vertebrae, cardiovascular defects, genitourinary, gastrointestinal and respiratory abnormalities as well as neurodevelopmental disorders [Slaney et al., 1996]. Strikingly, the p.(Ser252Trp) substitution leads to cleft palate more frequently, while the p.(Pro253Arg) substitution leads to more severe syndactyly [Slaney et al., 1996]. The latter may be caused by enhanced keratinocyte growth factor receptor-mediated signaling [Oldridge et al., 1999].

Heterozygous mutations in *FGFR2* can also lead to Crouzon syndrome (OMIM 123500). Crouzon syndrome is an autosomal dominant disease. It is estimated that 94% of *FGFR2* mutations occur in IgIIIa (exon 8; NM_000141.4), in IgIIIc (exon 10), or in the intron sequence flanking IgIIIc [Muenke and Wilkie, 2000] as cited in Kan et al. [2002]. The syndrome is characterized by craniosynostosis (ranging from single-suture synostosis to pansynostosis), exorbitism, and midface hypoplasia. Digital anomalies are not seen [Reardon et al., 1994; Glaser et al., 2000].

Pfeiffer syndrome (OMIM 101600) is an autosomal dominant disease. The syndrome is genetically heterogeneous [Muenke et al., 1994; Robin et al., 1994]; it is caused by mutations in *FGFR1* [Muenke et al., 1994] and *FGFR2* [p.(Trp290Cys), p.(Tyr340Cys), p.(Cys342Arg), p(Ser351Cys)] [Lajeunie et al., 1995b, 2006; Schell et al., 1995]. Some state that Pfeiffer and Crouzon syndrome contribute to the same spectrum of craniosynostosis and digital disorders that are caused by identical mutations in *FGFR2* [Rutland et al., 1995; Meyers et al., 1996].

Pfeiffer syndrome has been characterized by craniosynostosis, midface hypoplasia, hypertelorism, exorbitism, downslanting palpebral fissures, choanal stenosis or atresia, hand and foot anomalies (broad first digits, partial syndactyly of fingers and toes, brachymesophalangy), radiohumeral synostosis, Arnold Chiari malformation, hydrocephalus, congenital airway malformations, tracheal cartilage anomalies, deafness, and occasional cognitive impairment [Moore et al., 1995] as cited by Naveh and Friedman [1976], Cunningham et al. [2007], and Greig et al. [2013]. It has a relatively high mortality, and multiple surgical interventions are needed. Patients can be stratified in 3 categories (Cohen I–III or Greig A–C, based on increasing clinical severity). Expression is variable, some only show hand anomalies, while others have hand and skull anomalies [Baraitser et al., 1980; Sanchex and De Negrotti, 1981].

Jackson-Weiss syndrome (OMIM 123150) is an autosomal dominant disorder with high variability and high penetrance [Jabs et al., 1994]. Six different mutations have been identified in patients with the clinical diagnosis of this syndrome [Heike et al., 2001]. However, others state that Jackson-Weiss designation probably is best reserved for the original family segregating the p.(Ala344Gly) mutation [Kan et al., 2002]. The syndrome is characterized by craniosynostosis, foot anomalies (broad great toes with medial deviation, broad short metatarsals, broad proximal phalanges, partial cutaneous syndactyly of second and third toes, and tarsal-metatarsal coalescence), normal thumbs, hypertelorism, proptosis, and midface hypoplasia [Jabs et al., 1994; Heike et al., 2001].

Beare-Stevenson cutis gyrata syndrome (OMIM 123790) is an autosomal dominant disorder that was first described by Beare et al. [1969] and Stevenson et al. [1978]. It was further delineated by Hall et al. [1992]. Przylepa et al. [1996] identified 2 specific point mutations in *FGFR2*, p.(Ser372Tyr) and p.(Tyr375Cys), as the genetic cause. The syndrome is characterized by craniosynostosis (cloverleaf skull in over half of the patients), facial features similar to Crouzon syndrome, choanal stenosis or atresia, cutis gyrata, and significant developmental delay as summarized in Wenger et al. [2015]. Additional reported physical features include a prominent umbilical stump, acanthosis nigricans, skin tags, hirsutism, hypertelorism, proptosis, palatal abnormalities, and genitourinary abnormalities, including anteriorly placed anus, hypoplastic labia, and hypospadias [Wenger et al., 2015]. Also, a high rate of sudden unexplained death is reported (13/21 cases died before the age of 1 year). All surviving patients had a tracheostomy [Wenger et al., 2015].

Bent-bone dysplasia (OMIM 614592) is a recently recognized perinatal lethal skeletal dysplasia syndrome. It is caused by autosomal dominant mutations in *FGFR2*, p.(Tyr381Asp) and p.(Met391Arg), and is characterized by low-set ears, hypertelorism, midface hypoplasia, micrognathia, prematurely erupted fetal teeth, and clitoromegaly [Merrill et al., 2012; Scott et al., 2014]. Radiographic findings include bent long bones, osteopenia, ir-

regular periosteal surfaces (especially in the phalanges), deficient skull ossification, coronal synostosis, and hypoplastic clavicles and pubis [Merrill et al., 2012].

FGFR3

Muenke syndrome (OMIM 602849) is an autosomal dominant syndrome caused by one specific mutation in *FGFR3*, p.(Pro250Arg). The mutation rate at this nucleotide is estimated at 8×10^{-6}, one of the highest described in the human genome [Moloney et al., 1997]. The mutation occurs in the linker region between the second and third extracellular immunoglobulin-like domains [Moloney et al., 1997]. Ibrahimi et al. [2004] have shown that the Pro250Arg mutation causes enhanced ligand binding, especially to FGF9, while this was not the case for FGF7 or FGF10. Possibly this explains why the limb phenotype of Muenke syndrome is less severe than that of Apert syndrome. Muenke syndrome is characterized by bilateral or unilateral coronal synostosis, specific bone anomalies of the hands and feet (carpal and tarsal fusion, coned epiphyses, and broad toes), midface hypoplasia, high-arched palate, ptosis, and downslanting palpebral fissures. Sensorineural hearing loss is reported [Bellus et al., 1996; Muenke et al., 1997; Doherty et al., 2007; Agochukwu et al., 2012a]. Also, feeding and swallowing difficulties, developmental delay [Doherty et al., 2007], and epilepsy occur [Agochukwu et al., 2012b]. There is striking inter- and intrafamilial variability and reduced penetrance, where some of the mutation carriers did not show any signs of craniosynostosis, having only macrocephaly or even normal head sizes [Bellus et al., 1996; Muenke et al., 1997].

Crouzon syndrome with acanthosis nigricans (OMIM 612247) is an autosomal dominant disorder caused by a specific mutation in *FGFR3*, p.(Ala391Glu) [Meyers et al., 1995]. The condition is characterized by clinical features of Crouzon syndrome (craniosynostosis, ocular proptosis, and midface hypoplasia) and acanthosis nigricans [Meyers et al., 1995; Arnaud-López et al., 2007], but notably, choanal atresia or stenosis and hydrocephalus occur much more frequently. Acanthosis nigricans comprises verrucous hyperplasia and hypertrophy of the skin with hyperpigmentation and accentuation of skin markings, especially in flexural areas [Meyers et al., 1995].

TWIST1

Saethre-Chotzen syndrome (OMIM 101400) is an autosomal dominant disorder with high penetrance [Howard et al., 1997] due to mutations in the basic helix-loop-helix transcription factor *TWIST1* [Howard et al., 1997]. Mutations include SNPs, small indels, and large deletions [Johnson et al., 1998; Zackai and Stolle, 1998; Gripp et al., 2000; Chun et al., 2002]. These mutations lead to haploinsufficiency, altering osteoblast apoptosis [Yousfi et al., 2002], possibly through direct interaction with the DNA-binding domain of RUNX2 [Fitzpatrick, 2013] resulting in inhibition of RUNX2 function [Yousfi et al., 2002]. RUNX2 is a dosage-sensitive regulator of calvarial osteogenesis [Mundlos et al., 1997; Lou et al., 2009]. Also, *TWIST* may affect the transcription of fibroblast growth factor receptors [Howard et al., 1997]. Saethre-Chotzen is characterized by coronal synostosis, dysmorphic facial findings (facial asymmetry, hypertelorism, maxillary hypoplasia, high forehead, low-set frontal hairline, strabismus, ptosis, prominent ear crus, low-set posteriorly rotated small ears, conductive hearing loss, deviated nasal septum, and cleft palate), limb abnormalities (such as brachydactyly and cutaneous syndactyly), and mild to moderate mental retardation [Howard et al., 1997]. Also, there may be a predisposition to early-onset breast cancer [Sahlin et al., 2007].

Recently, mutations in *TWIST1* resulting in a specific missense substitution have been associated with Sweeney-Cox syndrome (OMIM 617746), characterized by frontonasal dysplasia and hand malformations (syndactyly and long fingers with relatively short distal phalanges held in fixed flexion), bilateral talipes equinovarus, bilateral undescended testes, imperforate anus, and mild intellectual disability [Kim et al., 2017].

ERF

ERF-related craniosynostosis (OMIM 600775) is an autosomal dominant disorder explained by mutations in the *ERF* gene. *ERF* encodes an inhibitory ETS transcription factor that directly binds to ERK1/2 [Mavrothalassitis and Papas, 1991; Sgouras et al., 1995; Le Gallic et al., 1999, 2004; Polychronopoulos et al., 2006; von Kriegsheim et al., 2009], 2 extracellular signal-related kinases that are involved in mitogen-activated protein kinase signaling downstream of RAS [Plotnikov et al., 2011; Twigg et al., 2013b]. Haploinsufficiency of *ERF* possibly results in the inability to inhibit RUNX2 function [Fitzpatrick, 2013; Twigg et al., 2013b]. Reduced dosage of ERF causes (late-onset) multisuture or sagittal suture synostosis, craniofacial dysmorphisms (hypertelorism, shortening and/or vertical displacement of the nose, and prominent orbits and forehead), Chiari malformation, mild hand anomalies, and language delay [Twigg et al., 2013b].

Recently, a specific recurrent missense mutation in *ERF* has been associated with Chitayat syndrome (OMIM 617180; hyperphalangism, characteristic facies, hallux valgus, and bronchomalacia but without craniosynostosis) [Balasubramanian et al., 2017].

TCF12

TCF12-related craniosynostosis (OMIM 615314) is an autosomal dominant disorder with substantial nonpenetrance (>50%) that can be caused by mutations in *TCF12* [Sharma et al., 2013]. The product of the gene is a member of the basic helix-loop-helix E-protein family and forms heterodimers with TWIST1 [Connerney et al., 2006; Sharma et al., 2013]. The disorder is explained by haploinsufficiency [Sharma et al., 2013] due to point mutations [Sharma et al., 2013; di Rocco et al., 2014; Paumard-Hernández et al., 2015] or large intragenic rearrangements [Goos et al., 2016] of *TCF12*.

TCF12-related craniosynostosis leads to coronal synostosis; in 32% of the cases with bicoronal and in 10% of the cases with unicoronal synostosis and previous negative genetic testing, a mutation could be identified [Sharma et al., 2013]. In addition to coronal synostosis, craniofacial features suggestive of Saethre-Chotzen syndrome are frequently described, and a minority has developmental delay and/or learning disabilities. Furthermore, analysis of a group of mutation-positive patients shows that they often need only one surgical procedure and that raised intracranial pressure after the initial surgical procedure is rarely observed. Patients with *TCF12*-related craniosynostosis generally appear to have a benign clinical course [Sharma et al., 2013].

EFNB1

Loss-of-function mutations in *EFNB1* can lead to CFNS (OMIM 304110) [Twigg et al., 2004, 2006; Wieland et al., 2004, 2005, 2008; Wieacker and Wieland, 2005; Davy et al., 2006; Shotelersuk et al., 2006; Vasudevan et al., 2006; Wallis et al., 2008; Hogue et al., 2010; Makarov et al., 2010; Zafeiriou et al., 2011; Apostolopoulou et al., 2012]. Paradoxically, this X-linked disorder is more prominent in heterozygous females than in hemizygous males. The mechanism underlying this phenomenon is suggested to be cellular interference [Twigg et al., 2004, 2013a; Wieacker and Wieland, 2005]. *EFNB1* encodes ephrin-B1, which is a transmembrane ligand for Eph receptor tyrosine kinases involved in cell-cell interaction [Klein, 2004]. Due to random X-inactivation, heterozygous females have random patterns of expressing and nonexpressing cells leading to ectopic cell boundaries, while all cells are nonexpressing in hemizygous males, leading to a less severe phenotype. In contrast, mosaic males show a more severe phenotype as they have a wild-type to mutant ratio similar to that in heterozygous CFNS females [Twigg et al., 2006, 2013a; Wieland et al., 2008]. A cohort study has shown that all patients with CFNS have hypertelorism, a certain degree of longitudinal ridging and/or splitting of nails, webbed neck, clinodactyly of one or more toes, and abnormal facial proportions [van den Elzen et al., 2014]. A bifid tip of the nose; indentation of the columella; a low implant of breasts; rounded, sloping, and often rather narrow shoulders with a reduced range of motion; facial asymmetry; aberrant shape of the eyebrow; broad nasal bridge, and craniosynostosis are often seen [van den Elzen et al., 2014]. Hence, CFNS manifests features of both craniosynostosis and craniofacial clefting.

Methods

In 2015, Twigg et al. wrote a review comprising 57 known genes that were mutated in ≥2 patients with craniosynostosis. To add all novel causative genes described from then on, we searched the Embase and PubMed databases, using the search term "craniosynostosis." The search was performed from January 2015 until December 2017.

We included all English articles that mentioned causative genes in their abstracts or titles. In order to include all relevant information, we also selected reviews. In case of a novel causative gene, further information on the gene was gained by inserting the gene in PubMed (https://www.ncbi.nlm.nih.gov/) and OMIM (https://omim.org/).

Results

Our search resulted in 204 records. Thirty-nine novel craniosynostosis genes were identified between January 2015 and December 2017 that cause craniosynostosis. Twenty-two mutations were identified in multiple patients and 17 in single patients. We will focus on the genes mutated in multiple patients. An overview of mutations in multiple patients and single patients is given in Tables 1 and 2, respectively.

B3GAT3

In 6 patients from 4 unrelated consanguineous families, a unique homozygous mutation in the *B3GAT3* gene

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; Kaname 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

Table 1 (continued)

	Gene	OMIM	Location	Clinical disorder	Major phenotypic features	Inheritance pattern	Prevalence of CSO with mutation	First references
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.

was identified [Yauy et al., 2018]. During the prenatal period, Antley-Bixler syndrome was clinically suspected [Yauy et al., 2018]. The patients had craniosynostosis, midface hypoplasia, bilateral radioulnar synostosis, multiple neonatal fractures, dislocated joints, joint contracture, long fingers, foot deformities, and cardiovascular abnormalities [Yauy et al., 2018]. All patients died before 1 year of age [Yauy et al., 2018]. Homozygous mutations in *B3GAT3* have been described as linkeropathies [Bloor et al., 2017]. These linkeropathies are characterized by their enzymatic inability to synthesize the common linker region of glycosaminoglycans, which joins the core protein with its respective glycosaminoglycan side chain [Mizumoto et al., 2015] as cited in Bloor et al. [2017]. Proteoglycans are crucial for effective communication between cells [Bloor et al., 2017].

CD96

A de novo balanced translocation, 46,XY,t(3;18)(q13.13;q12.1), was identified in a boy with C syndrome/Opitz trigonocephaly (OMIM 211750) [Chinen et al., 2006]. Resequencing this gene in 9 Japanese patients with C syndrome revealed an additional de novo missense mutation in one [Kaname et al., 2007]. However, the results could not be confirmed by a mutation screen of *CD96* by Sanger sequencing of 20 Caucasian individuals with C syndrome. C syndrome/Opitz trigonocephaly phenotypically overlaps with Bohring-Opitz syndrome (caused by mutations in *ASXL1*) [Hoischen et al., 2011] and is characterized by trigonocephaly, unusual facies, wide alveolar ridges, multiple buccal frenula, limb defects, visceral anomalies, redundant skin, psychomotor retardation, and hypotonia [Gorlin and Hennekam, 2001] as cited by Kaname et al. [2007]. The clinical picture is highly variable [Peña-Padilla et al., 2017]. *CD96* encodes a member of the immunoglobulin superfamily. Possibly, mutations in *CD96* affect cell adhesion and cell growth [Kaname et al., 2007].

DPH1

In 4 individuals from a North American genetic isolate and 4 individuals of a nonrelated consanguineous Saudi Arabian family, homozygous mutations were identified in *DPH1* [Alazami et al., 2015; Loucks et al., 2015]. The patients had developmental delay, central nervous system malformations (including Dandy-Walker malformations, cerebellar vermis hypoplasia, and posterior fossa cysts), dysmorphic features (including scaphocephaly, prominent forehead, hypertelorism, downslanting palpebral fissures, epicanthal folds, low-set ears, depressed nasal bridge, micrognathia, and sparse scalp hair), ventricular septal defect, short stature, and early lethality [Alazami et al., 2015; Loucks et al., 2015]. DPH1 is involved in the biosynthesis of diphthamide [Liu et al., 2004]. *Dph1*-deficient mice die perinatally and show restricted growth, developmental defects, cleft palate, and craniofacial abnormalities [Chen and Behringer, 2004; Yu et al., 2014].

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

Table 2 (continued)

	Gene	OMIM	Location	Clinical disorder	Major phenotypic features	Inheritance pattern	Prevalence of CSO with mutation	First references
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

[a] Incidence in 1 patient with craniosynostosis. AD, autosomal dominant; AR, autosomal recessive; CSO, craniosynostosis; C2/3, 2nd and 3rd vertebrae of the spinal cord; ID, intellectual disability; OI, osteogenesis imperfecta, OP, osteopetrosis; OSA, obstructive sleep apnoea; XLD, X-linked dominant.

FGF9

A heterozygous missense mutation in *FGF9* was identified in a proband and his father. Both had sagittal suture synostosis, proptosis, syndactyly, and broad thumbs. The father also had synostosis of interphalangeal, carpal-tarsal and lumbar vertebral joints [Rodriguez-Zabala et al., 2017]. Previously, a different heterozygous missense mutation was identified in a family of 12 affected members with synostosis of the interphalangeal, carpal-tarsal, humeroradial and lumbar vertebral joints [Wu et al., 2009]. Rodriguez-Zabala et al. [2017] state that their mutation impairs the ability of FGF9 to homodimerize and bind to its receptor FGFR2, leading to impaired FGF signaling.

FTO

In a consanguineous Palestinian Arab family (9 affected individuals), a Tunisian (1 affected individual), and a Yemeni family (2 affected individuals), homozygous missense mutations were identified in *FTO* [Boissel et al., 2009; Daoud et al., 2016; Rohena et al., 2016]. The affected individuals had postnatal growth retardation, microcephaly, severe psychomotor delay, functional brain deficits, and characteristic facial dysmorphism. In some patients, structural brain malformations, cardiac defects, genital anomalies, and cleft palate were also observed. Early lethality resulting from intercurrent infections or unidentified causes occurred at 1–30 months of age [Boissel et al., 2009]. One patient had craniosynostosis; 7 patients had skull asymmetry [Rohena et al., 2016]. FTO belongs to the AlkB-related dioxygenase family [Gerken et al., 2007]. The molecular mechanism leading to the severe polymalformation syndrome seen in the affected patients remains unclear. Possibly, FTO plays a role in genome integrity [Boissel et al., 2009].

HNRNPK

In several individuals, loss-of-function mutations have been identified in *HNRNPK* [Au et al., 2015; Lange et al., 2016; Miyake et al., 2017]. Additionally, 2 individuals with deletions of 9q21 encompassing *HNRNPK* have been reported (9q21.32q21.33) [Pua et al., 2014; Hancarova et al., 2015]. *HNRNPK* haploinsufficiency causes Au-Kline syndrome (OMIM 616580), a Kabuki-like syndrome [Lange et al., 2016; Miyake et al., 2017]. Affected individuals show intellectual disability, a shared unique craniofacial phenotype (long palpebral fissures, ptosis, broad prominent nasal bridge, hypoplastic nasal bridge, hypoplastic alae nasi, open downturned mouth, cupid's bow, full lower lips, ears with underdeveloped and thick helices, and a median crease in the tongue), structural brain anomalies, and connective tissue and skeletal abnormalities (high palate, scoliosis, extra lumbar vertebrae, hip dysplasia, hyperextensibility, cardiac and aortic anomalies as well as craniosynostosis). Also, decreased sweating, hypotonia, and mild

oligodontia have been reported [Pua et al., 2014; Au et al., 2015; Hancarova et al., 2015].

The exact disease mechanism remains unclear; however, hnRNP K recently has been implicated in synaptic plasticity through its effects on ERK kinase cascade activation [Folci et al., 2014].

IFT140

Compound heterozygous and homozygous mutations in *IFT140* were identified by Perrault et al. [2012] in several individuals of 6 families affected with Mainzer-Saldino syndrome. Mainzer-Saldino syndrome is a rare autosomal recessive disease defined by phalangeal cone-shaped epiphyses, chronic renal disease, nearly constant retinal dystrophy, and mild radiographic abnormality of the proximal femur [Beals and Weleber, 2007]. Occasional features include: short stature, cerebellar ataxia, and hepatic fibrosis [Beals and Weleber, 2007]. Two affected individuals had microcephaly, 1 had microcephaly with scaphocephaly, and 1 had only scaphocephaly [Perrault et al., 2012]. Heterozygous mutations were also identified in individuals with similar phenotypes, suggesting that other *IFT140* mutations in unscreened regions (e.g., deep intronic mutations) can add to the phenotype [Perrault et al., 2012]. Perrault et al. [2012] also identified mutations in an individual with Jeune syndrome. Recently, biallelic mutations were identified in *IFT140* in a Mexican proband with C syndrome/Opitz trigonocephaly (see *CD96* for the clinical phenotype) [Peña-Padilla et al., 2017].

IFT140 encodes one of the subunits of the intraflagellar transport complex A involved in the genesis, resorption, and signaling of primary cilia [Perrault et al., 2012].

IGF1R

Six case reports of trisomy (or tetrasomy) of chromosome 15q25qter (including *IGF1R*) in individuals with craniosynostosis draw the attention to *IGF1R* as a gene involved in premature suture fusion [Pedersen, 1976; Van Allen et al., 1992; Van den Enden et al., 1996; Zollino et al., 1999; Hu et al., 2002; Nagai et al., 2002].

A resequencing study by Cunningham et al. [2011] identified 5 variants in *IGF1R* in patients with isolated sagittal or coronal suture synostosis (with 3 variants being exclusive and 2 found to be rare).

IGF1R is a tyrosine kinase growth factor receptor that serves as the receptor for IGF-I and IGF-II [Cunningham et al., 2011]. Al-Rekabi et al. [2016] state that IGF1 activation mediates changes in cellular contractility and migration in osteoblasts of patients with single-suture craniosynostosis.

KAT6B

Two male patients with sagittal suture synostosis and a phenotype of Lin-Gettig syndrome had de novo frameshift mutations in *KAT6B* [Bashir et al., 2017]. The patients had hypoplastic male genitalia, agenesis of the corpus callosum, thyroid abnormalities, and dysmorphic features which include short palpebral fissures and retrognathia [Bashir et al., 2017].

Previously, *KAT6B* mutations have been identified in genitopatellar syndrome (OMIM 606170) and Say-Barber-Biesecker-Young-Simpson syndrome (OMIM 603736) [Bashir et al., 2017].

MASP1

Homozygous mutations have been identified in *MASP1* in individuals with Carnevale, Malpuech, and Michels syndrome [Rooryck et al., 2011; Atik et al., 2015; Urquhart et al., 2016]. These syndromes contribute to the 3MC syndrome (OMIM 257920). 3MC syndrome is an autosomal recessive heterogeneous disorder with features linked to developmental abnormalities. The main features include facial dysmorphism, craniosynostosis, cleft lip/palate high-arched eyebrows, hypertelorism, developmental delay, and hearing loss [Urquhart et al., 2016]. Besides *MASP1*, *COLEC11* has been identified as a genetic cause of 3MC syndrome. Both genes encode for proteins that play important roles in the lectin complement pathway [Degn et al., 2012].

NFIA

One patient with developmental delay, macrocephaly, hypoplastic corpus callosum, metopic synostosis, and hematuria has been described with an intragenic microdeletion of exons 4–9 of *NFIA* [Rao et al., 2014]. Additionally, a family (a father and 3 children) had a 109-kb deletion of chromosome 1p31.3 (deleting exons 1 and 2 of *NFIA*) [Nyboe et al., 2015]. Their phenotype comprised sagittal or lambdoid suture synostosis, macrocephaly, developmental delay and mild mental retardation, overgrowth, bilateral proximally placed first fingers, and low-set ears [Nyboe et al., 2015]. MRI scans showed hypoplasia of the corpus callosum, ventriculomegaly, herniation of cerebellar tonsils, absent falx cerebri, and in 1 case partial incomplete inversion of the left hippocampus [Nyboe et al., 2015]. Furthermore, renal defects were observed (including hydronephrosis, hydrourethra, and renal cysts) [Nyboe et al., 2015]. NFIA is a member of the Nuclear Factor I family of transcription factors. Disruption of *Nfia* in mice results in perinatal lethality, severe communicating hydrocephalus, a full-axial tremor, and agenesis of the callosal body [das Neves et al., 1999].

P4HB

Two unrelated individuals with Cole-Carpenter syndrome (OMIM 112240; comprising frequent fractures, craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features) had the same heterozygous missense mutation in *P4HB* [Rauch et al., 2015]. In 1 individual, the mutation arose de novo, whereas in the other, the mutation was transmitted from the clinically unaffected father, who is a mosaic carrier of the variant [Rauch et al., 2015]. A third patient with an identical mutation was identified by Balasubramanian et al. [2018] (not present in the mother, and the sample of the father was not available for analysis). Metadiaphyseal "crumpling" fractures with metaphyseal sclerosis in the long tubular bones may be an indicator of this specific genotype [Balasubramanian et al., 2018]. The exact pathophysiology is not clear yet. *P4HB* encodes for protein disulfide isomerase (PDI), which is involved in endoplasmic reticulum stress [Rauch et al., 2015]. Possibly, maintenance of a functional extracellular matrix is affected [Balasubramanian et al., 2018].

BRAF and PTPN11

Previously, mutations in *KRAS* have been identified in patients with Noonan syndrome (OMIM 613706) and craniosynostosis [Takenouchi et al., 2014; Addissie et al., 2015]. Ueda et al. [2017] presented more patients with RASopathies and craniosynostosis. They identified mutations in *PTPN11* in 3 unrelated patients with Noonan syndrome and sagittal synostosis and mutations in *BRAF* in 4 patients with cardiofaciocutaneous syndrome (all 4 had sagittal and/or lambdoid synostosis) [Ueda et al., 2017]. The exact etiology remains unclear; however, there might be a possible interaction between FGFR and the RAS/MAPK signaling pathways [Takenouchi et al., 2014; Addissie et al., 2015].

RSPRY1

Four siblings of a consanguineous Saudi family had a homozygous 1-bp duplication in *RSPRY1* that predicted frameshift and premature truncation [Faden et al., 2015]. They all showed a skeletal dysplasia phenotype, comprising progressive spondyloepimetaphyseal dysplasia (OMIM 616723), short stature, microcephaly and facial dysmorphisms (hypertelorism, epicanthal folds, mild ptosis, strabismus, malar hypoplasia, short nose, depressed nasal bridge, full lips, small low-set ears and short neck), short fourth metatarsals, intellectual disability, delayed motor development, and generalized hypotonia. All siblings had craniosynostosis. An additional mutation in *RSPRY1* was identified in an unrelated Peruvian index with a similar phenotype, but without craniosynostosis [Faden et al., 2015]. There is not much known about the function of RSPRY1 [Faden et al., 2015]. However, strong RSPRY1 protein localization in murine embryonic osteoblasts and periosteal cells during primary endochondral ossification suggests a role in bone development [Faden et al., 2015].

SCN4A

Two brothers of a nonconsanguineous East Indian family had compound heterozygous mutations in *SCN4A*. They had lower facial weakness, high-arched palate, sagittal and metopic synostosis, axial hypotonia, proximal muscle weakness, and mild scoliosis [Gonorazky et al., 2017]. Also, atrophy of the gluteus maximus, adductor magnus, and soleus muscles was seen. Muscle biopsy of the younger sibling revealed myofibers with internalized nuclei, myofibrillar disarray, and "corona" fibers [Gonorazky et al., 2017]. Electrophysiological characterization of the mutations revealed full and partial loss of function of the $Na_v1.4$ channel, which leads to a decrement of the action potential and subsequent reduction of muscle contraction [Gonorazky et al., 2017]. Previous reports of compound heterozygotes of mutations in *SCN4A* did not describe craniosynostosis [Ptácek et al., 1992; Jurkat-Rott et al., 2000; Tsujino et al., 2003; Vicart et al., 2004; Zaharieva et al., 2016], and the craniosynostosis phenotype cannot be explained by loss of function of the $Na_v1.4$ channel [Gonorazky et al., 2017]. Therefore, craniosynostosis may be an incidental finding in these 2 siblings.

SLC25A24

In 3 girls with Gorlin-Chaudhry-Moss syndrome (OMIM 233500) and 2 girls with Wiedemann-Rautenstrauch syndrome (OMIM 264090), 2 recurrent de novo mutations were identified in the *SLC25A24* gene [Ehmke et al., 2017]. Three out of 5 individuals had proven coronal synostosis [Ehmke et al., 2017]. Other features observed were severe midface hypoplasia, body and facial hypertrichosis, microphthalmia, short stature, short distal phalanges, lipoatrophy, and cutis laxa [Ehmke et al., 2017]. The same mutations were also identified in 4 cases with Fontaine syndrome (OMIM 612289), 2 of them had craniosynostosis [Writzl et al., 2017]. Ehmke et al. [2017] assume that the mutations influence the formation or opening of the mitochondrial permeability transition pore leading to an increased sensitivity of the mitochondria to oxidative stress.

SMAD6 and BMP2

Timberlake et al. [2016] tested 191 patients with sagittal and/or metopic synostosis. Seventeen probands had mutations in *SMAD6*. Ten parents had a mutation in *SMAD6*, without craniosynostosis, indicating striking incomplete penetrance [Timberlake et al., 2016]. In a genome wide association study of nonsyndromic sagittal synostosis, a SNP near *BMP2* (rs1884302) had a strong signal [Justice et al., 2012]. Genotyping of this SNP in the *SMAD6* mutation-positive individuals provides strong evidence of epistatic interaction between *SMAD6* and *BMP2*. This 2-locus model is estimated to be the genetic cause in approximately 3.5% of all the craniosynostosis cases [Timberlake et al., 2016], and the results have been replicated by Timberlake et al. [2017]. Activation of BMP receptors leads to phosphorylation of receptor SMADs, which can complex with SMAD4, translocate to the nucleus, and partner with RUNX2 to induce transcription of genes that promote osteoblast differentiation [Hata et al., 1998; Javed et al., 2008] as summarized by Timberlake et al. [2016]. This can be inhibited by SMAD6, and SMAD6 can also inhibit BMP signaling [Murakami et al., 2003]. Haploinsufficiency of SMAD6 thus leads to loss of the inhibitory effect of SMAD6, promoting increased BMP signaling and premature closure of sutures [Timberlake et al., 2016].

SMO

In 8 patients with phenotypical features of Curry-Jones syndrome (OMIM 601707), recurrent somatic mosaicism was identified for a nonsynonymous variant in *SMO*, p.(Leu412Phe) [Twigg et al., 2016].

Curry-Jones syndrome comprises patchy skin lesions (including streaky skin lesions, nevus sebaceous, and trichoblastoma), polysyndactyly, diverse cerebral malformations (including medulloblastoma), unicoronal synostosis, iris colobomas, microphthalmia, and intestinal malrotation with myofibromas or hamartomas [Twigg et al., 2016]. *SMO* encodes a frizzled G-protein-coupled receptor that plays a key role in transduction of Hedgehog signaling [Twigg et al., 2016]. The aforementioned substitution has been shown to constitutively activate SMO in the absence of Hedgehog signaling [Sweeney et al., 2014; Atwood et al., 2015].

SOX6

A de novo balanced translocation t(9;11)(q33;p15) was identified in a patient of German origin. The breakpoint on chromosome 11p15 was located in the *SOX6* gene. The phenotype of the patient comprised synostosis of the lambdoid sutures and the distal part of the sagittal suture with a gaping anterior fontanelle, proptosis, midfacial hypoplasia, flat supraorbital ridges, a high forehead, downslanting palpebral fissures, low-set and posteriorly rotated ears as well as muscular hypotonia. Mutation screening of *SOX6* in 104 craniosynostosis patients revealed a heterozygous missense mutation in a patient with sagittal and coronal suture synostosis which was inherited from his clinically unaffected mother. Since *SOX6* plays a critical role in chondrogenesis, it remains a gene of interest [Lefebvre et al., 1998; Smits et al., 2001; Akiyama et al., 2002; Lefebvre, 2002; Ikeda et al., 2004].

ZNF462

Eight members from 6 families were identified to have loss-of-function variants in *ZNF462* [Weiss et al., 2017]. They had ptosis, metopic ridging, craniosynostosis, dysgenesis of the corpus callosum, and developmental delay [Weiss et al., 2017].

Discussion

In 2015, fifty-seven human genes had been described for which there is evidence that mutations are causally related to craniosynostosis (based on at least 2 affected individuals with congruent phenotypes) [Twigg and Wilkie, 2015]. During the following years, a further 39 genes have been identified that can cause craniosynostosis (22 in multiple patients and 17 in single patients). An overview of these genes is given in Tables 1 and 2.

Many of the genes act in previously described pathways that are involved in the biology of cranial suture development, such as the Sonic hedgehog pathway, WNT-signaling, NOTCH/EPH pathway, the RAS/MAPK pathway, Indian hedgehog, Retinoic acid, and/or the STAT3 pathway. These are classical pathways that are involved in early embryonic development. But also, many of the gene defects may act through causing perturbations in osteogenesis, such as filaminopathies, hypophosphatasia [Currarino, 2007; Murthy, 2009], mucopolysaccharidoses [Ziyadeh et al., 2013], osteosclerosis [Kato et al., 2002; Kwee et al., 2005; Simpson et al., 2007, 2009], and pycnodysostosis [Osimani et al., 2010; Bertola et al., 2011; Berenguer et al., 2012; Caracas et al., 2012; Twigg and Wilkie, 2015]. These diagnoses include potentially treatable conditions, for which early recognition is particularly important [Wilkie et al., 2017], and more and more mutations are being identified in genes that are involved in brain development or that are associated with intellectual disability

and/or behavioral anomalies (such as *ASXL1*, *ANKDR11*, *KAT6A*, *KMT2D*, and *ZEB2*) [Twigg and Wilkie, 2015]. In the latter 2 groups, craniosynostosis often does not occur in all affected individuals.

Miller et al. [2017] classified causative mutations according to 4 categories: mutations in commonly mutated craniosynostosis genes, in other core craniosynostosis genes, more rarely associated genes, and known disease genes not known to be associated with craniosynostosis [Miller et al., 2017]. Next-generation sequencing of DNA of 40 probands and, if available, DNA of their parents, identified mutations in all 4 categories, making an argument for the value of next-generation sequencing instead of gene-specific testing [Miller et al., 2017; Wilkie et al., 2017].

Also, the first evidence for a digenic disease mechanism has been described; rare mutations have been identified in *SMAD6* (an inhibitor of BMP) in combination with a common SNP near *BMP2* (rs1884302) in patients with midline craniosynostosis [Timberlake et al., 2016]. If confirmed, the interaction of a rare and a common variant would have major implications for variant filtering using frequencies. Furthermore, it has implications for diagnostics as patients with midline craniosynostosis are not routinely tested [Wilkie et al., 2017]. But most importantly, it indicates that craniosynostosis can be a complex trait, with mutations in several genes leading to the specific phenotype.

In conclusion, the phenotypes associated with newly identified mutations are less specific and some are very rare. This, in combination with the increasing number of potential genetic causes and the possibility of digenic disease mechanisms indicate the importance of next-generation sequencing [Twigg and Wilkie, 2015; Miller et al., 2017; Wilkie et al., 2017].

Disclosure Statement

The authors have no conflicts of interest to disclose.

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