Review Article

Genetics and the role it plays in craniofacial anomalies

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Abstract: Craniofacial anomalies are a group of common congenital anomalies. They include orofacial clefts and craniosynostosis, which each may occur as an isolated anomaly or as part of a syndrome. There are hundreds of syndromes associated with craniofacial anomalies. Here we review a few select syndromes including 22q11.2 deletion syndrome, Van der Woude syndrome, Stickler syndrome, Trisomy 13, CHARGE syndrome, ectodermal dysplasias, Kabuki syndrome, and acrocephalosyndactyly syndromes. While most syndromes are associated with genetic etiologies, even isolated anomalies often have genetic components. Determining whether the anomaly is isolated, or part of a syndrome can provide prognostic, management, and recurrence information for families. The care team for an individual with a craniofacial anomaly includes a multitude of different subspecialists from a variety of fields including plastic surgery, oral and maxillofacial medicine, audiology, speech language pathology, otolaryngology, neurosurgery, genetics, pediatrics, social work, nutrition, and sleep medicine. A multidisciplinary care approach is beneficial, and ideally the care team can work together, communicate, and understand the different goals and scope of each team member. Genetics clinicians are a crucial part of the care team to determine the etiology of the anomaly and to inform the family and other subspecialists. Although the literature surrounding the genetic etiology of craniofacial anomalies continues to expand, limitations remain in the current understanding of genetic and other factors contributing to craniofacial anomalies.

Keywords: Cleft lip; cleft palate; craniosynostosis; genetic syndromes; nonsyndromic

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Introduction

Background

Orofacial clefts (OFC) and craniosynostosis are common craniofacial anomalies. OFCs can be separated into two distinct categories, cleft lip with or without cleft palate (CLP) and cleft palate alone (CPO). In the United States, the population prevalence of OFC is approximately 1 in 1,000 and 1 in 1687 for CLP and CPO, respectively (1). CPO can involve both the hard and soft palate, or the soft palate alone and can be considered V-shaped or U-shaped. U-shaped cleft palate can be present with micrognathia and glossoptosis causing airway obstruction. This triad is referred to as Pierre Robin Sequence, although the original definition by Dr. Pierre Robin in 1923 did not include cleft palate in the triad (2-4). CLP can have a variety of phenotypes including unilateral, bilateral, complete, and incomplete (5). CLP incidence varies by ancestry and is

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most prevalent in individuals of Asian ancestry, followed by Caucasian, and least prevalent in individuals of African ancestry. CLP is more common in males, and CPO is more common in females (6-8). OFC incurs significant healthcare costs and is associated with long-term impacts on feeding difficulties, speech, hearing, dental problems, and possible psychological difficulties (9).

Craniosynostosis is a disorder present at birth which consists of premature closure of one or more of the cranial sutures. It is an important condition to recognize and surgically treat in most cases to allow for proper brain growth and development. With proper monitoring and treatment, intelligence will be unaffected. Overall incidence of craniosynostosis is 1 in every 2,000 to 2,500 live births. It affects all races and ethnicities equally, as well as females and males equally overall, although sagittal craniosynostosis occurs in a 2:1 ratio for males to females (10).

There are multiple types of craniosynostosis, affecting different sutures. The suture involved can be predicted by the shape of the infant's skull. The most common is sagittal synostosis in which the infant will have scaphocephaly, or a long and narrow head shape. Coronal synostosis is the second most common type and can occur on one side only or on both sides of the head. In bilateral coronal synostosis one sees a broad and tall skull shape (turribrachycephaly), while if only one suture is affected, one sees an asymmetric skull shape (plagiocephaly). More rare causes include lambdoid and metopic craniosynostosis, where there will be posterior plagiocephaly or trigonocephaly, narrow in front and wide in the back, respectively (10-12). Oxycephaly, or cloverleaf skull, is the fusion of most or all cranial sutures (13).

Rationale

There are multiple subspecialists involved in the care of individuals with craniofacial anomalies, each bringing their own expertise to the care team. However, it is important for each subspecialist to understand the role and scope of the other providers, as well as stay current on advances in the field. This review is to provide a broad overview of the role genetics plays in the care of individuals with craniofacial anomalies for providers in oral and maxillofacial medicine.

Objective

This study is to review the clinical genetics of craniosynostosis and cleft lip and palate.

Embryology

OFC

CLP and CPO are two distinct entities with different embryological mechanisms. The lips begin to develop at approximately the 4th week gestation with formation of maxillary and frontonasal prominences. Next, the nasal placodes are formed from the nasal processes. In the 6th and 7th week gestation, the upper lip is formed from the fusion of the maxillary prominences and nasal processes (14). When the fusion fails between the nasal and premaxillary prominences, the cleft lip defect occurs (15). This often extends to the anterior hard palate, which may subsequently prevent the soft palate from forming at 63 days gestation by the fusion of the lateral palatine processes. In this case, the cleft palate occurs as a downstream effect of the cleft lip. Whereas CPO is from a separate mechanism and not a downstream effect of cleft lip. CPO occurs later in development after the lip has already been fused (15). It is important to consider CLP and CPO as two different defects within the OFC spectrum with different recurrence risks, associated syndromes, and counseling points.

Craniosynostosis

The embryological formation of the cranial vault begins in the precondensation phase of the embryonic phase. In this phase the fetal head gains mesenchymal cells from both cranial neural crest cells (NCCs) and paraxial mesoderm. Paraxial mesoderm aids in the formation of the parietal, occipital and petrous temporal bones. NCC mesenchyme gives rise to the squamous temporal, parietal, sphenoid and frontal bones. They also play a role in signaling the growth of the sutures and underlying meninges. It is the condensation of the mesenchymal cells, which contain osteoprogenitor cells, that gives rise to the ectomeningeal membrane, which is the first sign of the cranial vault at around day 30 of gestation. Intramembranous ossification then occurs to form the individual bones around week 7–8 in the fetal phase of development. Calcification then occurs via osteoblast cells to form spicules which radiate outward and form the first type of bone tissue, called woven bone, which will be gradually replaced by lamellar bone by the time of birth (16).

The cranial sutures form as a fibrous tissue in between the forming membranous bones, which are guided by the formation of dural reflections. By the 16th week of development, the bones have reached the sites of the dural

reflections and the outward expansion of the bones towards the periphery slows down to leave the unossified connective regions between the bones, forming the sutures. These sutures are maintained via interaction between the regulated osteoprogenitor cells at the edge of the forming bones, called the osteogenic front, and the underlying dura via intracellular signals such as fibroblast growth factor (FGF), mechanical signals and cell migration into the sutures. When this signal cascade is altered and these bone fronts prematurely fuse, craniosynostosis arises (16).

Genetics evaluation

Accurate assessment of the underlying cause of an individual's craniofacial disorder is crucial for both patient health and safety and for genetic counseling. The National Society of Genetic Counselors (NSGC) defines genetic counseling as "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease" (17). Both craniosynostosis and OFC can either be non-syndromic, lacking other associated clinical features, or can be part of an underlying syndrome (18,19). There are more than 300 syndromes that are associated with OFC (15). Approximately 70% of CLP and 50% of CPO are isolated, while the remainder may be syndromic or associated with other abnormalities (18). CPO is more likely to be syndromic compared to CLP (5). Even in cases of isolated, non-syndromic cases of OFC, there are still genetic components (15) and often complex multifactorial mode of inheritance with a combination of genetic and environmental factors (20).

Cleft palate, even when isolated, is associated with an increased risk of speech difficulties, facial growth differences, feeding issues, and recurrent otitis media. These complications warrant evaluation by multiple specialists. However, if the OFC is part of a known genetic syndrome, prognosis and medical management recommendations would be dependent on the syndrome (15). As an example, for a child with cleft palate secondary to 22q11.2 deletion syndrome, there are published medical management guidelines to be followed in their care that may be different from those with isolated cleft (21,22).

Recurrence risk estimates are different for syndromic versus non-syndromic clefts (23). If a syndrome or causative gene variant is identified, recurrence risk is based on known inheritance pattern associated with that syndrome or gene. For example, genetic conditions associated with autosomal dominant (AD) inheritance have a 50% recurrence risk for the affected individual. Parents of the affected individual can also consider genetic testing for the variant. If neither parent harbors the variant, the recurrence risk for their own subsequent pregnancies is difficult to estimate but is often cited at approximately 1% due to the chance of germline mosaicism (24). In non-syndromic cases, principles of multifactorial inheritance and empiric risk estimates can be discussed (25). The empiric recurrence risk for apparently non-syndromic CLP is estimated to be between 4% and 10% (26).

The role of the geneticist and genetic counselor is to identify if an individual's cleft is an isolated anomaly or syndromic (27). To determine if a cleft is likely to be isolated or syndromic, a careful dysmorphological exam, a 3-generation pedigree, and thorough discussion of medical and developmental history is necessary (23,27). Dysmorphology is the study of human malformations and can help identify rare syndromes by focusing on physical features that may be suggestive of a difference in fetal development (28-30). Genetic conditions often have subtle characteristic physical features that may be missed by those who are not specifically trained in dysmorphology. This exam includes assessment of major and minor anomalies. A major anomaly is one that has major medical, social, or cosmetic consequences, OFC being an example. Minor anomalies are more common in the general population, and do not independently have health consequences but may represent a divergence of typical development, such as widely spaced eyes or single palmar crease (30,31). Multiple major anomalies occurring together, one major anomaly and multiple minor anomalies, or three or more minor anomalies would all increase suspicion for syndromic etiology (30). Another important aspect of the physical exam is to evaluate the premaxillary segment. Cleft defects with underdevelopment or absence of the premaxillary segment are sometimes referred to as median CLP (15). Median CLP can be associated with holoprosencephaly (HPE), a congenital brain malformation with varying degrees of severity (32). HPE has been associated with trisomy 13 and monogenic causes (15,33).

Dysmorphology can provide definitive diagnoses (29). However, genetic testing is now available to confirm many suspected diagnoses, or for a broader evaluation when dysmorphology examination is not able to provide a diagnosis. If there is suspicion of a syndromic etiology of the cleft, the geneticist or genetic counselor can facilitate genetic testing with the family.

After decades of research, genetic etiology of OFC is not fully understood. Concordance rates in twin studies suggest a significant genetic component to OFC (34). Several studies investigating genetics of non-syndromic clefts have found multiple novel susceptibility genes and pathways, copy number variants (CNVs), loci with OFC subtype-specific effects, and novel loci involving transcription factors (35-38). A recent study found rare disease gene variants in 17% of their cohort with non-syndromic isolated cleft palate (25). In addition to many genetic factors that have been identified, careful consideration must also be given to possible influence from environmental exposures or maternal teratogens (26). Environmental factors that have been associated with increased risk of OFC include tobacco smoking (39-41), alcohol (39,42,43), maternal diabetes (44), and certain antiepileptic drugs (45). Epigenetic factors are the subject of recent research efforts to aid in current understanding in the development of clefts. Epigenetics is the study of heritable non-coding sequence alterations that impact gene expression (46). Recent studies suggest that epigenetics may impact the occurrence and penetrance of clefting (47,48). One study suggested a gene-environment interaction between maternal environmental tobacco smoke and *IRF6* single nucleotide polymorphisms (SNP) (49).

It is common to encounter families with multiple members in different generations with non-syndromic OFC. These cases raise suspicion of AD monogenic etiology for the clefting. Regardless of whether genetic testing can identify the causative variant, there may be some degree of reduced penetrance (50-52). Reduced or incomplete penetrance means that some individuals with the gene variant will not exhibit the associated phenotype (53). In these scenarios, recurrence risk of clefting is challenging to estimate, since it is unknown what percentage of people with the specific variant will be affected with a cleft. AD non-syndromic clefting with reduced penetrance is an important topic to be discussed with patients with positive family history.

Similarly to OFC, craniosynostosis can be divided into non-syndromic (isolated) or syndromic. Approximately 15% of cases are syndromic. Of all genetic cases, 50% are due to new, *de-novo*, pathogenic variants and the other half are inherited, most commonly in an AD fashion. Similarly to OFC, there are still genetic components of non-syndromic cases which are most likely multifactorial and also include environmental contributions such as maternal smoking, fetal positioning, maternal thyroid disease and teratogen exposures (10,13).

Syndromic and non-syndromic cases of craniosynostosis have vastly different implications for the patient and family, including prognosis, potential complications, management recommendations, and recurrence risk assessment. If a genetic variant is established and syndrome is diagnosed, it is important to make sure the patient has had screenings and care for the other associated health problems with that syndrome. For certain syndromes, there may even be treatment options if a diagnosis is established. For non-syndromic cases of craniosynostosis, genetic diagnosis can still aid in prognosis and give family answers as to why the sutures closed prematurely and recurrence rate for future children (54). For example, in 2010, Wilkie *et al.* (55) found that patients with *FGFR3* P250R variant or *TWIST1* variants had a more severe course and required re-operation as compared to patients with other variants such as *TCF12* or chromosomal abnormalities. They, therefore, recommend at minimum, testing of *FGFR2* P250R and *FGFR2* exons IIIa/c for patients with coronal or multi suture craniosynostosis (56). In Albright osteodystrophy, caused by pathogenic variants in *GNAS1*, often the first sign of disease is craniosynostosis. Later in life, round face, short stature, dental abnormalities, and ossification of subcutaneous tissue becomes more apparent. For these patients, monitoring of calcium and parathyroid hormone levels is crucial and treatment with phosphate restriction, calcium supplementation and calcitriol is usually necessary (57).

Recently, several single gene variants have been identified in cases of non-syndromic craniosynostosis in studies utilizing whole genome sequencing for affected patients. It is important to note that the penetrance for these variants is often incomplete, leading to highly variable phenotypes among patients. *FGFR2*, *FGFR3*, *LRIT3*, *ALX3*, *TCF12* and *TWIST1* are genes that have been identified in non-syndromic and syndromic craniosynostosis. Pathogenic variants in these genes perturb the FGFR signaling pathway and cause syndromic and non-syndromic craniosynostosis through a variety of mechanisms. A detailed discussion is beyond the scope of this review, but more information is available in references (58,59). Wilkie *et al.* [2010] reported that pathogenic variants in *FGFR3* was the most common in all cases with an established genetic cause. Conversely, isolated sagittal and metopic stenosis have <1% yield in genetic testing (54-56). They also found that patients with coronal craniosynostosis were more likely to have a genetic variant established during testing than other types of craniosynostosis. Variants in several other genes, some including *IGFR1* and *FREM1*, have also been identified

in isolated craniosynostosis. While their role in suture development is less defined, it is thought that *FREM1* may also play a role in the FGF pathway by binding to FGFs (54).

Genetic testing

OFC

Genetic testing for OFC has been done for patients with suspected syndromic clefting, although emerging evidence suggests considering genetic testing for isolated non-syndromic cases (25). Geneticists and genetic counselors can review benefits, limitations, and utility of testing on a case-by-case basis. When genetic testing is pursued, chromosomal microarray (CMA) is often the first-line test performed. This testing is often recommended as the initial test for a multitude of indications including multiple congenital anomalies, autism spectrum disorders, and non-syndromic developmental delay and intellectual disability (58). CMAs evaluate for CNVs, which are gains or losses of genetic material. There are different types of CMA technologies that each have specific nuances in terms of resolution and types of genetic variation they can detect (60-65). When ordering testing, it is important for the ordering provider to understand which platform is offered by the lab, and the associated benefits and limitations. Additional consideration must be given to any follow up testing that may be warranted in the event of an abnormal result, such as parental studies, or determining if the CNV arose from an inherited unbalanced chromosomal rearrangement (60).

Although CMAs are broad, genome-wide analyses, they do not detect all types of genetic abnormalities, and a negative CMA cannot rule out the possibility of a genetic condition. Specifically, CMAs do not detect sequence variants, repeat expansion disorders, or methylation defects. If clinical suspicion remains high for syndromic etiology after a non-diagnostic CMA, sequence-based testing may be considered. Sequence-based tests may be ordered as single gene analysis, disease-targeted panel testing, or broad-based testing such as exome or genome sequencing. Practice guidelines released by the American College of Medical Genetics and Genomics (ACMG) in 2021 recommend exome and genome as first- or second-tier testing for individuals with one or more congenital anomalies (66). Exome sequencing evaluates the protein-coding regions of the genome, where most pathogenic variants that contribute to Mendelian disorders can be found (67). A 2019 meta-analysis found the diagnostic yield of exome sequencing to be 53% for individuals with neurodevelopmental disorders with other associated conditions (68). Several recent studies have utilized exome sequencing to find susceptibility genes for individuals with non-syndromic cleft lip with or without cleft palate, and cleft palate alone (69-71). The broad approach of exome and genome sequencing requires detailed phenotypic information about the patient so the laboratory can appropriately filter the data and interpret the results of testing. It is crucial for the clinical team to provide the lab with this information (72).

Craniosynostosis

To date, over 50 genes have been established that contribute to craniosynostosis, isolated and syndromic. While three-quarters of established genetic diagnoses come from six of those genes, there is still importance in testing for other less common genetic variants when the suspicion for a syndrome is high. Most start with testing of the most common causes: *FGFR2* exons IIIa and IIIc, *FGFR3* exon 7 and *TWIST1* exon 1 and an array CGH, which is useful in detecting chromosomal abnormalities and CNVs, which can detect deletions of the genes involved in suture formation (54). If a diagnosis is not established while testing for those, then providers can opt to test for more rare genetic causes, while understanding that there is significant heterogeneity among the less common genetic causes. Many providers opt to start broader instead, by ordering a gene panel that includes testing of up to 65 of the genes associated with craniosynostosis. It is important to recognize when using the gene panels that a negative result does not rule out a genetic cause, as through genome sequencing, new genetic causes for craniosynostosis are still being established that have not been included on gene panels yet. Arguments for using a broader gene panel include limiting lab draws and providing better care to patients that have rarer syndromes that may not be picked up on otherwise and may have treatment options that are crucial to start early in life (54-56).

The cost of genomic sequencing has greatly reduced since the first human genome was sequenced as part of the Human Genome Project due to new sequencing technology. It is thought that the cost of this sequencing may continue to reduce due to advancements in technologies and strategies (73). In a 2020 qualitative study involving executives from 14 US insurance payer companies, a majority said pediatric exome sequencing is covered in the case of congenital anomalies and neurodevelopmental

disorders and acknowledged the overall need of the testing due to its ability to improve clinical interventions and provide a diagnosis (74).

For all genetic testing, pre-test genetic counseling is important to set appropriate expectations for the patient/family. Pre-test counseling should include purpose of testing, benefits and limitations, possible result types including uncertain, incidental, and optional choices such as secondary findings, cost to the patient/family, insurance coverage, and implications of the results for the patient and family members (66,75). There should be a shared clinician-patient/family decision making process regarding genetic testing (66).

Select syndromes: OFC

22q11.2 deletion syndrome

22q11.2 deletion syndrome is the most common deletion syndrome, occurring in 1 in 4,000 births. This AD condition is associated with more than 180 different clinical features (76-82). Each individual with 22q11.2 deletion syndrome has a different combination of features, and presentation is highly variable within and between families (83). Common features include conotruncal heart defects, palate abnormalities, immunodeficiency, characteristic facial features, learning and developmental disabilities, hypocalcemia, renal anomalies, and psychiatric conditions (21,81,83-87). Others include hearing loss, gastrointestinal, ophthalmologic, genitourinary, skeletal, and central nervous system anomalies (21). Palate abnormalities associated with 22q11.2 deletion syndrome are commonly velopharyngeal insufficiency, cleft palate, submucous cleft palate, and bifid uvula (21). This condition was described multiple independent times by physicians, thus 22q11.2 deletion syndrome has historically been assigned many names, including velo-cardio-facial syndrome (VCFS), DiGeorge syndrome, conotruncal anomaly face syndrome, and later 22q11.2 deletion syndrome (83). Approximately 90% of individuals with a 22q11.2 deletion have the deletion happen spontaneously. The remaining cases are inherited (88,89). Given the variability of the condition, it may not be obvious if a parent is affected or not, and therefore, testing parents is always indicated (88).

Van der Woude syndrome (VWS)

One of the most common syndromes including OFC as a predominant feature is VWS (90,91). Pathogenic variants in the *IRF6* gene cause VWS and popliteal pterygium syndrome (PPS) (92-94). The *GRHL3* gene has also been identified as a causative gene for VWS and a candidate gene for non-syndromic CLP (95). VWS is associated with mixed clefting and lower-lip fistulae (pits). Mixed clefting means some individuals may have CLP, and some may have CPO. About 10–20% of cases may also have hypodontia (96). In the absence of lip pits, VWS is clinically indistinguishable from non-syndromic clefting. The PPS phenotype includes CLP, lip pits, popliteal pterygia, syndactyly, pyramidal skin on hallux, and genital abnormalities including bifid scrotum, cryptorchidism, and hypoplasia of the labia majora. There are some genotype phenotype correlations for different *IRF6* variants, some causing VWS phenotype and some causing PPS (96).

Stickler syndrome

Stickler syndrome is a connective tissue disorder that has cleft palate as a primary feature, including Pierre-Robin sequence, cleft soft or hard palate, or bifid uvula (97). Stickler syndrome exhibits variable expression within and between families (97,98). Other prominent features include characteristic facial features such as midface hypoplasia, broad or flat nasal bridge, and micrognathia, ocular abnormalities, hearing loss, and skeletal findings. Characteristic ocular findings are specific vitreous or retinal abnormalities (98). Most patients have myopia, usually severe, early onset, and non-progressive. Stickler syndrome is also well associated with cataracts (97,99). Diagnosis is important, because it is the most common inherited cause of rhegmatogenous retinal detachment in childhood (97). Hearing loss can be sensorineural or conductive. Skeletal findings include joint hypermobility and spondyloepiphyseal dysplasia (98). Of note, mitral valve prolapse is present in half of patients (100). There are both AD (*COL2A1*, *COL11A1*, *COL11A2*) and autosomal recessive forms (*COL9A1*, *COL9A2*, *COL9A3*) of Stickler syndrome. Stickler syndrome can be diagnosed based on clinical features, although there is not currently a consensus on clinical diagnostic criteria (98).

Trisomy 13

Trisomy 13 is a chromosomal abnormality associated with a spectrum of congenital anomalies (101). Trisomy 13 is typically associated with very limited survival, as the vast majority of infants die within the first few months of life. Longer term survivors have profound intellectual

disability, growth restriction, congenital heart defects, polydactyly, respiratory issues, OFC, abdominal wall defects, genitourinary defect, limb abnormalities, and central nervous system defects including neural tube defects, hydrocephalus, microcephaly, arhinencephaly/HPE. The CNS abnormalities are commonly midline defects (101-104). There are guidelines published to assist in the care of individuals with Trisomy 13 which require multidisciplinary care (101).

Given the high mortality rate associated with Trisomy 13, postnatal intervention has historically been limited. A 2016 study shows one-year and long-term survival rates to be higher than previously reported (105). The level of intervention that should be provided to an individual with Trisomy 13 has been a subject of much debate and research. This poses an ambiguous question, and one that may need to be individualized by case and viewed in the context of family-centered care (106).

CHARGE syndrome

CHARGE syndrome is an AD condition characterized by a spectrum of birth differences. CHARGE is an acronym explaining common features of the condition; *c*oloboma, *h*eart disease, *a*tresia of the choanae, *r*etarded growth and mental development, *g*enital anomalies, and *e*ar malformations and hearing loss. Most cases of CHARGE syndrome are caused by a variant in the *CHD*7 gene, and a majority occur *de novo*. After discovery of the genetic etiology of CHARGE syndrome, the spectrum of associated features has broadened to include many more features than the name acronym suggests. Other findings associated with CHARGE syndrome include abnormal ear shape, developmental delay, hypogonadotropic hypogonadism, renal malformations, OFC, tracheoesophageal anomalies, cranial nerve anomalies, vestibular defects, hypothyroidism, and brain anomalies (107-109).

Ectodermal dysplasias

Ectodermal dysplasias are conditions that impact two or more body parts derived from the ectoderm. This includes hair, teeth, nails, and sweat glands. These conditions may present with hypotrichosis, anodontia, hypodontia, sweating abnormalities, nail dysplasia, OFC, digital anomalies, ankyloblepharon, and developmental delay (110-114). The most common ectodermal dysplasia that includes OFC is *TP63*-related disorders, including ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) (115) syndrome Rapp-Hodgkin syndrome) (116), acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome (117), ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (EEC3) (118), limb-mammary syndrome, split-hand/foot malformation type 4 (SHFM4) (119), and isolated cleft lip/cleft palate (orofacial cleft 8) (111,112,114,120-124). These different ectodermal dysplasia conditions are characterized by distinct anomalies. A 2021 study by Ganske *et al.* investigating the prevalence and characteristics of OFC in individuals with ectodermal dysplasia suggested that *TP63* variants may account for a similar percentage of syndromic forms of OFC as VWS, Trisomy 13, and CHARGE syndromes (125).

Kabuki syndrome

Kabuki syndrome is associated with a wide range of clinical features. Kabuki syndrome is an AD condition when caused by *KMT2D* variants, and an X-Linked condition when caused by *KDM6A* variants. Clinical features associated with Kabuki syndrome include characteristic facial features, intellectual disability, and growth delay. The degree of intellectual disability is typically between mild to moderate, with severe being less common. However, intellectual disability is not always present. Congenital malformations are also common including heart defects, CLP, gastrointestinal abnormalities, skeletal abnormalities. Characteristic physical features include persistence of fetal fingertip pads, long palpebral fissures with eversion of the lateral third of the lower eyelid, broad and highly arched eyebrows, short columella, prominent ears. Individuals with Kabuki syndrome may also have hearing impairment, feeding difficulties, susceptibility to autoimmune conditions, seizures, and infantile hypotonia (126,127). Although CLP is a well-known association with Kabuki syndrome, a 2021 case series by Kim *et al.* suggests that submucous cleft palate may be more common in Kabuki syndrome than previously known (128). Other craniofacial features include palatal insufficiency, high-arched palate, hypodontia, and abnormally shaped teeth (126).

Syndromic craniosynostosis: acrocephalosyndactyly syndromes (Apert, Crouzon, Saethre-Chotzen, and Pfeiffer syndromes)

While they are rare, the syndromic forms of craniosynostosis, Apert, Crouzon, Saethre-Chotzen, and Pfeiffer syndromes, are among the most well-known genetic syndromes. These syndromes are part of a group of conditions known as

acrocephalosyndactyly syndromes (ACS), although today they are more commonly referred to as FGFR-related craniosynostosis conditions. ACS are associated with craniosynostosis, syndactyly of hand and/or feet, and may include various other anomalies (129).

Apert syndrome

Apert syndrome is caused by one of two variants in the *FGFR2* gene, specifically Ser252Trp and Pro253Arg variants, causing faulty communication between FGF and the receptor. These are sporadic variants in 95% of cases, while the other 5% are transmitted in an AD fashion, meaning the recurrence rate for future offspring would be 50%. Apert syndrome occurs in 1 out of every 65,000 births, has equal male and female distribution and the highest incidence in individuals of Asian ancestry. It is characterized by craniosynostosis, facial structure differences such as hypertelorism, or widely spaced eyes, bulging eyes, down-slanting palpebral fissures, maxillary hypoplasia, and limb and finger differences. Often, those with Apert syndrome will have syndactyly of the second through fourth fingers, "mitten-like" syndactyly, but can have other fusions as well such as in the toes, although upper extremities are usually impacted more severely as bones in the arm, wrist and cervical vertebrae can also be fused. These patients are often impacted by developmental delays and mild to moderate intellectual disability. Their brains may have autonomic nervous system malformations and absent corpus callosum as well as other brain midline defects, and hearing loss. Some patients have also had tracheal malformations, cardiac, and gastrointestinal anomalies (130). Therefore, these patients will need a multidisciplinary team and will need to have audiology and ophthalmology evaluations as well as an airway evaluation with possible sleep study, echocardiogram if murmur or clinical signs are present, renal ultrasound, CT of sutures with 3D reconstruction and CT of cervical vertebrae as well as brain MRI and hand radiographs (131). Patients with Apert syndrome have varied phenotypes ranging from mild to severe and many, with proper follow-up and supportive care, are able to live normal adult lives without reduction in life expectancy (130).

Crouzon syndrome

Crouzon syndrome is also caused by variants in the *FGFR2* gene, and over 50 different *FGFR2* variants are known to cause the Crouzon phenotype. The p.Ala391Glu variant of *FGFR3* is known to cause Crouzon syndrome with the addition of acanthosis nigricans. In Crouzon syndrome, 70% of cases are inherited through AD transmission, with the rate of recurrence being 50%. It is worth noting that it has variable expressivity and incomplete penetrance. The remaining 30% of cases are sporadic variants. It occurs in 1 out of every 60,000 births and is the most common form of syndromic craniosynostosis. Crouzon syndrome is generally classified by craniosynostosis, most commonly coronal, midface hypoplasia and proptosis. Hearing loss is also common in up to 55% of cases and C2-C3 vertebral fusions have also been reported in up to 30% of cases. In these patients, limbs are generally spared, and normal intelligence can be expected, if there is timely surgical intervention for the craniosynostosis. Ophthalmologic evaluation is recommended due to the high incidence of exposure keratitis or conjunctivitis due to proptosis, as is audiology evaluation and sleep study due to maxillary hypoplasia (132).

Pfeiffer syndrome

Pfeiffer syndrome is another AD condition that is caused by variants in either of the *FGFR1*, for type I Pfeiffer syndrome, or *FGFR2* genes for type I, II and III. Pfeiffer syndrome occurs in 1 out of every 100,000 individuals and as indicated above, can be divided into types I, II and III (133). In type I, affected individuals tend to have craniosynostosis, hypertelorism, maxillary and midface hypoplasia, and dental abnormalities. They can also have broad thumbs and great toes but generally have normal intelligence. Variants in the *FGFR1* gene tend to have a milder phenotype (133,134). Type II is characterized by a cloverleaf skull, a severe form of craniosynostosis, which is often associated with hydrocephalus. Patients also have characteristic facial features including proptosis, midface hypoplasia and a "beak-shaped" nose. Those affected can also have ankylosis, or immobile elbow joints, and often have cognitive and respiratory impairment due to the severity of the craniosynostosis (133,134). Pfeiffer syndrome type III shares many characteristics with type II, except these individuals do not have the cloverleaf skull. They might, in addition, have shortened anterior cranial fossa base, natal teeth, more severe proptosis and abdominal anomalies such as hypoplastic gallbladder, pelvic kidney and hydronephrosis. Similarly to type II, cognitive impairment is common and these patients have also reported neurological maldevelopment with the development of seizures (133,134). All cases of type III and the majority of type II arise from

de novo variants (135). For all types of Pfeiffer syndrome, a sleep study and cranial imaging is recommended, and providers may want to consider abdominal ultrasound for type III to screen for visceral organ defects.

Muenke syndrome

Muenke syndrome is another syndromic cause of craniosynostosis, not part of the ACSs, caused by a *FGFR3* variant. It is inherited in an AD fashion and occurs in one out of 300,000 births. Muenke syndrome has high phenotypic variability, and some patients may not have any features of the condition, making it difficult to assess the percentage of variants that are inherited versus *de novo*. Affected patients can have a spectrum of craniosynostosis of all or multiple sutures with clover leaf skull to no fused sutures at all. They also have hypertelorism, mild proptosis, high arched palate with or without cleft lip and palate, fusion of the carpal or tarsal bones, broad toes and thumbs, brachydactyly and clinodactyly. They also can have strabismus, hearing loss in anywhere from 30–100% of patients, developmental delay and intellectual disability, and seizures (136). As with the other syndromes described, patients with Muenke syndrome will need ophthalmology and audiology evaluations, as well as early intervention for any developmental delay.

Saethre-Chotzen syndrome (SCS)

SCS is the one ACS that is not associated with variants in an *FGFR* gene. It is caused by variants *TWIST1* gene in most affected individuals, which is located at 7p21. This condition is thought to occur in 1 in every 50,000 births and is transmitted in AD fashion. Since SCS can present in the mild form, SCS may occur more often but is not diagnosed. Because of this, the percentage of cases that are inherited versus arising *de novo* are unknown. Those with SCS commonly have craniosynostosis with the distinct facial features of midface hypoplasia, mandibular hypoplasia, ptosis and hypertelorism. Some also have low-set ears, small pinna with prominent crus, absent teeth, supernumerary teeth, and a cleft palate. In addition to the facial differences, SCS is also characterized by syndactyly, specifically of the second and third fingers and toes. Patients may also have short fingers and clinodactyly, or abnormal bending of the fingers and may have fusion of vertebrae and radioulnar synostosis. It is worth noting that there are certain patient cases where only digit anomalies in the absence of craniosynostosis have been reported, as well as some affected with only craniosynostosis. Patients may also be affected by cryptorchidism, renal, and cardiac defects (137). Therefore, it is recommended to obtain an echocardiogram and renal ultrasound, audiology evaluation, sleep study and ophthalmologic evaluation annually as well as skull and vertebral imaging. Generally, cognitive development and intelligence is normal in patients with a *TWIST1* variant, however severe cognitive impairment may be present in patients with a deletion of the *TWIST1* gene and surrounding regions (138).

The strengths of this review is that it provides an overview of the literature by experts in the field, and a limitation is that there is additional information available that is beyond the scope of the information permitted in this review paper.

Conclusions

Craniofacial anomalies are common congenital anomalies and require multidisciplinary care for best treatment and outcomes. Genetics providers are an integral part of this care team to provide expertise in the genetic contributions to such anomalies. Craniofacial anomalies can be syndromic or non-syndromic, but both have genetic factors with varying inheritance patterns. Genetics providers provide care to families throughout the lifespan to help determine genetic etiologies of the craniofacial anomaly using physical exams, family history information, and genetic testing when appropriate. This provides important information such as diagnosis and prognosis, management implications, and recurrence risk for other family members.

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