Perspectives on craniofacial syndromes

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This article reviews syndrome classification; types of anomalies and their interrelations; syndrome delineation; birth prevalence; nomenclature; molecular delineation; and phenotype/genotype correlations.
☐ *Birth prevalence; craniofacial anomalies; craniofacial syndromes; deformations; disruptions; malformations; molecular genetics*

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Syndrome classification

There are many different ways to classify syndromes. Geneticists, orthodontists, craniofacial surgeons, oral and maxillofacial surgeons, and pediatricians all categorize syndromes in a different manner. There are probably as many methods of systematizing these disorders as there are clinicians and craniofacial biologists working in the field. Any attempt to bring order to a group of disparate conditions is helpful, even if various classifications cross-cut each other. Our own way of thinking about syndromes is summarized in Table 1.

Types of anomalies

Different types of anomalies are the building blocks of syndromes. Most anomalies observed at birth can be sorted into one of three basic categories—malformations, deformations, and disruptions. There are practical reasons for distinguishing these: the clinical implications of each category are different (Table 2) (1).

A malformation may be defined as a morphologic defect of an organ, part of an organ, or a larger area of the body resulting from an intrinsically abnormal developmental process. Polydactyly, cleft lip, or renal agenesis serve as examples. Malformations may be relatively simple or complex. The later the defect is initiated, the simpler the malformation. Malformations initiated earlier during organogenesis tend to have more far-reaching consequences (1).

A deformation may be defined as an abnormal form or position of a part of the body caused by nondisruptive mechanical forces. Important deformities include clubfoot, congenital hip dislocation, and congenital postural scoliosis. Deformations arise most frequently during late fetal life. Since the most common cause is intrauterine molding by mechanical forces, the musculoskeletal system is usually affected. The most important factor contributing to deformations is lack of fetal movement, whatever the cause. Deformations may result from mechanical, malformational, or functional causes (1).

First pregnancies tend to be associated with unstretched uterine and abdominal muscles, which may result in uteroplacental insufficiency, which in turn can lead to oligohydramnios. Breech presentation is common since the uterus is too compressed to allow the fetus to rotate into the cephalic position. Uterine restraints on fetal movement allow mild, but persistent, extrinsic forces to deform the fetus (1).

During the first few days after birth, infants with deformities can usually be folded into their atypical prenatal postures. Radiographically, the close correspondence between the abnormal posture of the fetus before delivery and the posture of the infant after birth has been observed repeatedly. Such posture has been termed the position of comfort. For example, a mandibular deformation may result from sharply lateroflexed position of the head with the shoulder pressed against the mandible for a long period of time late during intrauterine life (1).

A disruption is a morphologic defect of an organ, part of an organ, or a larger region of the body resulting from a breakdown of, or interference with, an originally normal developmental process. Examples include an amputation of a digit in utero caused by an amnionic band and other band-caused disruptions, such as ring constriction and distal pseudosyndactyly. In some cases amnionic bands can produce dramatic consequences, such as asymmetric encephaloceles, bizarre facial clefting, and limb amputations (1).

Interrelations between types of anomalies

It should be recognized that although the distinctions between the three types of anomalies—malformations,

Table 1. Classification of craniofacial syndromes

Morphologic
Clinical description
Developmental pathogenesis
Dysmorphic growth and development
Etiologic
Teratogenic
Chromosomal
Monogenic
Mendelian inheritance pattern
Molecular delineation

deformations, and disruptions—are useful for clinical purposes, particularly in the newborn period (Table 2), the three classes are interrelated in some instances during growth after birth. Sometimes classes overlap with growth and development, as with cleft lip/palate, resulting in secondary deformity (1).

Malformations can also result in deformations appearing at birth, such as bilateral renal agenesis, producing oligohydramnios and the facial and limb deformities of Potter sequence. Some anomalies, such as Robin sequence, may be malformational or deformational, depending on the initiating factor—intrinsic mandibular hypoplasia (malformational) or extrinsic mandibular constraint (deformational). Finally, some syndromes have both malformations and deformations or deformations and disruptions or a combination of all three. An analysis of these kinds of problems appears elsewhere (1).

Avoiding misconceptions

Medical geneticists and other clinicians approach patients from different perspectives. Therefore, it is important to clarify some of the thinking of medical geneticists (1).

We have distinguished malformations, deformations, and disruptions from each other. Craniofacial surgeons may use the term craniofacial deformities, and some oral and maxillofacial surgeons use the term dentofacial deformities. These are well-established usages in the surgical field. In medical genetics we recognize that surgeons use these terms generically. Dentofacial deformities may be deformations, malformations, or disruptions, and therefore they are very frequently combined. Some disruptions may have secondary deformations. If a hemifacial microsomia-like condition is produced in rodents by triazene or retinoids administered during pregnancy and postnatal growth is permitted to take place, deformations will occur secondarily to these disruptions. (In our field, teratogens are considered to cause disruptions, not malformations.) In conclusion, it is important to note that in the newborn period, distinctions between malformations, deformations, and disruptions are important clinically, prognostically, and in terms of recurrence risk. In the surgical perspective and with growth and development, these distinctions are blurred (1).

In medical genetics a syndrome is recognized to represent multiple malformations occurring in embryonically noncontiguous areas. For example, a patient with a cleft lip/palate, genital malformations, and syndactyly of the third, fourth, and fifth toes is recognized as having a syndrome. In such a patient the overall pattern of these embryonically noncontiguous malformations is commonly diagnostic. In contrast the 'long face syndrome', 'torticollis-plagiocephaly sequence', or combination of hemifacial microsomia and secondary torticollis are not syndromes in the medical genetic sense, but are regional complexes resulting from various interactive factors (1). (If a renal anomaly and abnormal lung lobation occurred in addition, a medical geneticist would regard this combination as a syndrome.)

In conclusion, it is not that the medical genetic perspective is 'right' and the clinical perspective is 'wrong', or vice versa. The two perspectives are equally correct, and the same data can be placed in either perspective, depending on the clinical problem to be addressed (1).

Syndrome delineation

The process of syndrome delineation can be divided into the following stages: 1) unknown-genesis syndromes, including provisionally unique-pattern syndromes and recurrent-pattern syndromes; and 2) known-genesis syndromes, including pedigree syndromes, chromosomal

Table 2. General comparison of malformations, deformations, and disruptions

Features	Malformations	Deformations	Disruptions
Time of occurrence	Embryonic	Fetal	Embryonic/fetal
Level of disturbance	Organ	Region	Area
Perinatal mortality	+	−	+
Clinical variability of any given anomaly	Moderate	Mild	Extreme
Multiple causes of any given anomaly	Very frequent	Less common	Less common
Spontaneous correction	−	+	−
Correction by posture	−	+	−
Correction by surgery	+	−/+	+
Relative recurrence rate	Higher	Lower	Extremely low
Approximate frequency in newborns	2%–3%	1%–2%	1%–2%

Source: Cohen (1).

Table 3. Approximate birth prevalences of some craniofacial anomalies and syndromes*

Condition	Approximate birth prevalence (per 1 million births)
Anomalies	
Anencephaly	1000
Cleft lip with or without cleft palate (whites)	1000
Craniosynostosis	340
Holoprosencephaly (nonchromosomal)	60
Chromosomal syndromes	
Trisomy 13 syndrome	80
Trisomy 21 syndrome	1500
Monogenic syndromes	
Achondroplasia	30–60
Apert syndrome	15–16
Branchio-oto-renal syndrome	25
Cornelia de Lange syndrome	60–100
Crouzon syndrome	15–16
Neurofibromatosis, type 1	330–400
Oculo-auriculo-vertebral spectrum	180
Oral-facial-digital syndrome, type 1	20
Osteogenesis imperfecta (all types)	50
Waardenburg syndrome	20–30
Teratogenic syndromes	
Fetal alcohol syndrome	2000

* Birth prevalence comparisons are best when the denominator is held constant, so that numerators can be compared meaningfully. Using the number per 1 million births permits even rare syndromes to be compared using whole numbers instead of fractions (e.g. 0.04 per 10,000).
Source: Cohen (1).

syndromes, biochemical defect syndromes, and environmentally induced syndromes (1, 2).

In an unknown-genesis syndrome, the cause is simply not known. In a provisionally unique-pattern syndrome, several anomalies are observed in the same patient such that the clinician does not recognize the overall pattern of defects from his own experience, from searching the literature, or from consultation with the most learned colleagues in the field. A recurrent-pattern syndrome can be defined as a similar or identical set of anomalies in two or more unrelated patients (1, 2).

A known-genesis syndrome can be defined as several anomalies causally related on the basis of 1) occurrence in the same family or, less conclusively, the same mode of inheritance in different families, 2) a chromosomal defect, 3) a specific defect in an enzyme or a structural protein, or 4) an environmental factor. The term pedigree syndrome refers to known genesis on the basis of pedigree evidence alone; the basic defect itself remains undefined, although the condition is known to represent a monogenic disorder. Examples include autosomal dominantly inherited mandibulofacial dysostosis, autosomal recessively inherited Meckel syndrome, and oral-facial-digital syndrome I that has X-linked dominant inheritance, lethal in the male. Chromosomal syndromes are cytogenetically determined; they include trisomy 13 syndrome, del(18q) syndrome, and 49,XXXXY syndrome. In a biochemical-defect syndrome, specific enzymatic defects are known in recessive syndromes. The term is also meant to include specific defects in structural proteins as these became known in some of the dominant disorders. Examples include the autosomal recessively inherited Hurler syndrome and the X-linked recessive Lesch–Nyhan syndrome. An environmentally induced syndrome is defined in terms of the environmental

Table 4. Selected genetic disorders localized to specific regions on specific chromosomes

Name	Chromosome and region
van der Woude syndrome	1q32
Holoprosencephaly-2	2p21
Waardenburg syndrome, type 1	2q35
Morquio syndrome, type B (MPS IVB)	3p21–p14.2
Hurler, Hurler–Scheie, Scheie syndromes	4p16.3
Achondroplasia	4p16.3
Hypochondroplasia	4p16.3
Thanatophoric dysplasia, types 1 and 2	4p16.3
Rieger syndrome	4q25–q27
Diastrophic dysplasia	5q31–q34
Mandibulofacial dysostosis	5q32–q33.1
Cleidocranial dysplasia	6p21
Saethre–Chotzen syndrome	7p21
Greig cephalopolysyndactyly	7p13
Split hand/split foot, type 1	7q11.2
Osteogenesis imperfecta, several forms	7q21.3–q22.1
Holoprosencephaly-3	7q36
Pfeiffer syndrome-1	8p11.2–p12
Branchio-oto-renal syndrome	8q13.3
Cohen syndrome	8q22–q23
Basal cell nevus syndrome	9q31
Tuberous sclerosis-1	9q33–q34
Nail-patella syndrome	9q34
Apert syndrome	10q25.3–q26
Crouzon syndrome	10q25.3–q26
Pfeiffer syndrome-2	10q25.3–q26
Stickler syndrome	12q13.1–q13.3
Spondyloepiphyseal dysplasia congenita	12q13.1–q13.3
Kniest syndrome	12q13.1–q13.3
Sanfilippo syndrome (MPS III)	12q14
Marfan syndrome	15q21.1
Rubinstein–Taybi syndrome	16p13.3
Tuberous sclerosis-2	16p13.3
Morquio syndrome, type A (MPS IVA)	16q24.3
Neurofibromatosis, type I	17q11.2
Osteogenesis imperfecta, several forms	17q21.31–q22
Campomelic dysplasia-1	17q24.3–q25.1
Neurofibromatosis, type 2	22q11.21–q13.1
Focal dermal hypoplasia	Xp22.31
Chondrodysplasia punctata, X-linked recessive	Xp22.3
Kallmann syndrome	Xp22.3
Coffin–Lowry syndrome	Xp22.2–p22.1
Aicardi syndrome	Xp22
Cleft palate/ankyloglossia	Xq21.1–q21.31
Simpson–Golabi–Behmel syndrome	Xq26
Börjeson–Forssman–Lehmann syndrome	Xq26–q27
Fragile X syndrome	Xq27.3
Hunter syndrome (MPS III)	Xq27.3
Otopalatodigital syndrome, type I	Xq28
Chondrodysplasia punctata, X-linked dominant type	Xq28

Source: Cohen (1).

Table 5. Mutations in human craniosynostosis syndromes on fibroblast growth factor receptor 2 (FGFR2)

Syndrome	Phenotype	Nucleotide change	Amino acid substitution
Apert syndrome	Craniosynostosis, symmetric syndactyly of hands and feet, other anomalies	934C→G	Ser252Trp
		937C→G	Pro253Arg
		934–935CG→TT	Ser252Phe
Crouzon syndrome	Craniosynostosis, midface deficiency, ocular proptosis	493A→G	Tyr105Cys
		934C→T	Ser252Leu
		978T→C	Ser267Pro
		982insTGG	Thr268ThrGly
		1012G→T	Cys278Phe
		1037del9	ΔHisIleGln
		(CCACATCCA)	287–289
		1045A→C	Gln289Pro
		1047T→G	Trp290Gly
		1047T→C	Trp290Arg
		1053A→G	Lys292Glu
		1162A→G	Tyr328Cys
		1171A→T	Asp331Ile
		1190ins6	337ins2
		(GACGCT)	(AspAla)
		1191G→C	Gly338Arg
		1192G→A	Gly338Glu
		1197T→C	Tyr340His
		1203T→A	Cys342Ser
		1203T→C	Cys342Arg
		1204G→A	Cys342Tyr
		1204G→T	Cys342Phe
		1205C→G	Cys342Trp
		1210C→G	Ala344Gly
		1211G→A	Ala344Ala
		1219C→G	Ser347Cys
		1240C→G	Ser354Cys
		1245del9	ΔTrpLeuThr
		(TGGTTGACA)	356–358
Pfeiffer syndrome	Craniosynostosis, broad thumbs, broad great toes, other anomalies	934–936CGC→TCT	Ser252Phe/Pro253Ser
		1141A→C	Cys278Phe
		1141A→C	Asp321Ala
		1200A→C	Thr341Pro
		1203T→C	Cys342Arg
		1203T→A	Cys342Ser
		1204G→A	Cys342Tyr
		1204G→C	Cys342Ser
		1209G→C	Ala344Pro
		1254G→T	Val359Phe
		1263insTCAACA	ΔGly345-Pro361
		Acceptor splice site:	
		T(−3)G	Intronic
		A(−2)G	Intronic
		G(−1)C	Intronic
		G(+1)T, (1119G→T)	Ala314Ser

Source: Cohen (5, 6) (see for complete molecular referencing).

factor or causative teratogen. Since most well-studied teratogens produce a continuum of adverse outcomes, it is inappropriate to restrict definition to the more severe end of the phenotypic spectrum where a recognized syndrome emerges. The term fetal effects is often used to indicate the entire continuum of possible outcomes, especially those at the mild end of the phenotypic spectrum. Thus, dysmorphologists frequently speak of fetal alcohol effects or fetal hydantoin effects. Other examples of recognized human teratogens include vitamin A congeners, folate antagonist chemotherapeutic agents, coumarin anticoagulants, oxazolidinediones, and valproic acid (1, 2).

Significance of syndrome delineation

The significance of syndrome delineation cannot be overestimated. As an unknown-genesis syndrome becomes delineated, its phenotypic spectrum, natural history, and

inheritance pattern or risk of recurrence become known, allowing better patient care and family counseling. If the phenotypic spectrum is known, the clinician can search for suspected defects that may not be immediately apparent but may produce clinical problems at a later date, such as hemivertebra in the Goldenhar syndrome. If a certain complication can occur in a given syndrome, such as a Wilms tumor in the Beckwith–Wiedemann syndrome, the clinician is forewarned to monitor the patient for possible development of neoplasia. Finally, if the recurrence risk is known, the parents can be counseled properly about future pregnancies. This is especially important if the risk is high and the disorder is severely handicapping or disfiguring, has mental deficiency as one component, or has a dramatically shortened life span. Thus, syndrome delineation fosters good patient care (1, 2).

Birth prevalence of malformation syndromes

The term birth prevalence is preferable to incidence because malformations and malformation syndromes frequently result in embryonic and fetal death, and early pregnancy losses are not ascertainable. Thus, the population of malformed infants represents incomplete ascertainment of those affected individuals who survive until birth. The birth prevalences of selected malformations and syndromes are shown in Table 3 (1).

Syndrome nomenclature: the possessive case should not be used

The use of the possessive case in syndrome nomenclature is commonly found in the surgical literature: Apert's syndrome, Crouzon's syndrome, Pfeiffer's syndrome, and the like. The fact is that the possessive case in syndrome designations is not found in the genetic or major pediatric literature. It was abolished in 1971 in the fourth edition of *Current Medical Information and Terminology* (3). There is not one instance of apostrophe *s* in either the 1976 or the 1990 edition of *Syndromes of the Head and Neck*. For a long time use of the possessive case in syndrome nomenclature has not been permitted by the editorial policy of many journals: *Journal of Pediatrics, European Journal of Pediatrics, Lancet, American Journal of Medical Genetics, American Journal of Human Genetics, Clinical Genetics, Journal of Medical Genetics*, and *Clinical Dysmorphology*, to name a few (4).

The reason for deleting the apostrophe *s* in syndrome designations is straightforward. First, Apert syndrome was well described by a number of authors earlier, long before Apert's (proper use of the possessive case) classic publication. In fact, he cites such references in his original 1906 paper. Thus, Apert does not have any property rights to the disorder. Second, Apert syndrome has become more fully understood subsequently because of the work of others. Third, Apert was a French pediatrician who did not have the syndrome he described. Thus, Apert neither had nor owned the syndrome that bears his name (4).

Molecular delineation

In recent years gene mapping has been very successful (Table 4). With the newer techniques of molecular genetics, it has been possible to isolate the genes responsible for specific malformation syndromes and to identify their mutations in terms of nucleotide changes and amino acid substitutions. Fibroblast growth factor receptors (FGFRs) serve as examples. Table 5 shows the mutations of some common craniosynostosis syndromes on FGFR2, which is chromosomally localized on 10q25.3-q26. Only two mutations cause Apert syndrome, but a large number of different mutations can cause Crouzon syndrome and Pfeiffer syndrome (5, 6).

Genetic heterogeneity and phenotype/genotype correlations

A common problem arises from genetic heterogeneity—different genes at different chromosome locations may give rise to the same disorder. For example, Pfeiffer syndrome may be caused by a mutation on FGFR1 (found on chromosome 8) and by a number of mutations on FGFR2 (found on chromosome 10). In some instances the same mutation on the same gene may cause different disorders. For example, an Asp178Asn mutation on the PRNP gene (found on chromosome 20) can result in one subtype of familial Creutzfeldt–Jakob disease or in familial fatal insomnia. Similarly, some of the same mutations on FGFR2 can cause either Crouzon syndrome or Pfeiffer syndrome. It would be a mistake to conclude that, because they can be caused by exactly the same mutation, they represent variability of the same disorder. Pfeiffer syndrome breeds true in families and so does Crouzon syndrome. Therefore, other factors are involved that are not yet understood (5, 6).

The study of genotype/phenotype correlations demonstrates some interesting trends. The Ser252Trp mutation for Apert syndrome is more commonly associated with posterior cleft palate, whereas the Pro253Arg mutation tends to have more severe syndactyly. Pfeiffer syndrome tends to have more severe ocular proptosis and broader thumbs and great toes with mutations on FGFR2 than with the single known mutation on FGFR1 (5, 6).

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