Syndromes with Cleft Lip and Cleft Palate

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A series of tables is presented as a *diagnostic aid* for the clinician when he confronts a patient who has a *cleft lip* and/or *palate*, together with associated anomalies. The tables provide a rapid way of sorting through the recognized *syndromes with orofacial clefting* in search of a possible overall diagnosis. Today, 154 such syndromes are recognized. This is more than twice as many as were known in 1971. Undoubtedly, many new syndromes with orofacial clefting will be delineated in the future.

Isolated cleft lip and cleft palate are common malformations. Their epidemiologic, genetic, and pathogenetic characteristics have been reviewed elsewhere (Burdi et al., 1972; Drillien et al., 1970; Fraser, 1970, 1971; Gorlin et al., 1971a, 1976; Woolf, 1971). The purpose of this paper is to present a series of tables that can be used as a diagnostic aid when the clinician is confronted with a patient who has a cleft and other associated anomalies. The tables provide a rapid way of sorting through the recognized syndromes with orofacial clefting in search of a possible overall diagnosis. Given the diagnosis, the tables can also be used to find the frequency of clefting in the syndrome, other features of the syndrome, and pertinent references.

Frequency of Syndromes with Clefting

In 1970, it was noted that less than three per cent of all cases of clefting were associated with syndromes (Fraser, 1970), although the basis for this estimate was not given. In 1971, Gorlin et al. reviewed 72 syndromes in which clefting occurred. In 1976, we discussed approximately 117 syndromes with orofacial clefting (excluding lateral and oblique facial clefts and mandibular clefts) (Gorlin et al., 1976). The current paper tabulates 154 such conditions. Thus, syndrome delineation is a dynamic, ongoing process that results in rapid expansion of our knowledge. Today we are aware of more than twice as many syndromes with orofacial clefting as we were in 1971.

Use of Syndromes Tables

A summary of syndromes with cleft lip and cleft palate (Tables 2–7) is provided in Table 1. The total number of syndromes listed is 176. Lateral, oblique, and mandibular clefts have not been included nor has an attempt been made to include syndromes with congenital palatopharyngeal incompetence. Several conditions appear more than once in Tables 2 through 7. For example, the Stickler syndrome may include cleft palate (Table 3—Syndromes with Cleft Palate) or the Robin complex (Table 4—Syndromes with the Robin Complex). There are 22 such instances of duplication in Tables 2 through 7. These are subtracted from the total number of syndromes. Thus, we are left with 154 syndromes with clefting. However, this is an underestimate since some syndromes listed are etiologically heterogeneous. For instance, the Larsen syndrome has autosomal recessive etiology in some families and autosomal dominant inheritance in others. Nevertheless, in the total number of syndromes with clefting (154), the Larsen syndrome is counted only once. If we counted the conditions known to be etiologically heterogeneous more than once, the total number of syndromes would be somewhat increased.

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Table 1 also lists the syndrome breakdown by etiology. There are a total of 79 monogenic syndromes. There are approximately as many autosomal recessive syndromes (39) as there are autosomal dominant ones (35). The inheritance patterns of several monogenic syndromes are uncertain at the present time as, for example, in autosomal dominant vs X-linked dominant transmission. In such instances, only one mode of inheritance identifies the syndrome for inclusion in Table 1, although both possibilities are listed under "Etiology" in the tables of specific syndromes (Tables 2–7). There are few X-linked syndromes (5) or environmentally-induced syndromes (6), but there are many chromosomal syndromes (29).

Many syndromes of unknown genesis appear in Tables 2 through 7 with a total of 40 such syndromes appearing in the summary in Table 1. Obviously, many more syndromes of unknown genesis occur than appear in the tables. In order to be included in the tables as a syndrome of unknown genesis, associated anomalies either had to occur with some regularity or had to be especially distinctive in combination.

Table 2 presents syndromes with cleft lip and cleft palate. As an isolated defect, cleft lip with or without cleft palate is etiologically distinct from cleft palate (Fogh-Andersen, 1942). This distinction breaks down in some malformation syndromes. For example, in the autosomal dominant van der Woude syndrome in which clefts occur together with lip pits, an affected individual may have cleft lip, cleft lip and cleft palate, or cleft palate. The van der Woude syndrome is found in Table 2. Any syndrome in which a cleft palate is expressed without cleft lip ever occurring, as in the Larsen syndrome, is found in Table 3. Syndromes with cleft palate are much more common (77) than syndromes with cleft lip-palate (28).

Table 4 presents syndromes with the Robin complex (cleft lip, micrognathia, and glossoptosis). Once thought to constitute a specific syndrome, the Robin complex is now known to be nonspecific, occurring *sui generis* or as a component part of various syndromes (Cohen, 1976).

Table 5 presents chromosomal syndromes associated with cleft lip and cleft palate. The overwhelming majority of chromosomal syndromes show an increase in clefting. Other common abnormalities found in many chromosomal syndromes are psychomotor and mental retardation, growth deficiency, microcephaly, malformed ears, congenital heart defects, ocular hypertelorism, micrognathia, and cryptorchidism (Lewandowski and Yunis, 1975).

Syndromes with median cleft lip are presented in Table 6. There are three major types of median cleft lip. The form with the worst prognosis is premaxillary agenesis which is almost always associated with alobar holoprosencephaly, amentia, seizures, apnea, and a very early demise. A second type of median cleft lip results from persistence of the infranasal furrow which frequently accompanies a more generalized median facial dysrhaphia with ocular hypertelorism, widely spaced nostrils, and lack of elevation of the nasal tip. A third type, a pseudomedian cleft, occurs when the insertion of the maxillary labial frenum pulls up the middle part of the upper lip, as in oral-facial-digital syndrome I.

Table 7 lists the known associations of various abnormalities with cleft lip and cleft palate. An association may be defined as the

TABLE 1. Summary of syndromes with cleft lip and palate.

category	*number*
Syndromes with cleft lip-palate	28
Syndromes with cleft palate	77
Syndromes with the Robin complex	18
Chromosomal syndromes with clefts	29
Median cleft lip	7
Associations with clefting	17
Total number of syndromes listed in tables	183
Syndromes appearing in more than one table	−22
Total number of syndromes	154

Syndrome breakdown by etiology

Etiology	*Number*
Monogenic	79
Autosomal dominant	(35)
Autosomal recessive	(39)
X-linked	(5)
Environmentally-induced	6
Chromosomal	29
Unknown genesis	40
Total	154

TABLE 2. Syndromes with cleft lip-palate

syndrome	*striking features*	*relative frequency of cleft lip-palate in syndrome*	*etiology*	*references*
Monogenic Syndromes				
Appelt syndrome	Ocular hypertelorism, tetraphocomelia, enlarged penis or clitoris	Common	Autosomal recessive; some authorities consider this syndrome and the pseudothalidomide syndrome to be identical	Appelt et al., 1966
Bixler syndrome	Hypertelorism, microtia, ectopic kidneys, congenital heart defect, growth deficiency	Common	Autosomal recessive	Bixler et al., 1969
Bowen-Armstrong syndrome	Growth retardation, mental deficiency, abnormal electroencephalogram, syndactyly of toes (2–3, 4–5), hyperpigmented areas, oligodontia, ankyloblepharon filiforme adnatum	Apparently common	Autosomal recessive	Bowen and Armstrong, 1976
Clefting/ankyloblepharon syndrome	Ankyloblepharon filiforme adnatum	Common	Autosomal dominant	Gorlin et al., 1971a
Clefting/enlarged parietal foramina syndrome	Enlarged parietal foramina	Uncommon	Autosomal dominant	Gorlin et al., 1971a
Cryptophthalmos syndrome	Cryptophthalmos, abnormal frontal hairline, variable syndactyly of hands and feet, coloboma of alae nasi, genitourinary anomalies	Uncommon	Autosomal recessive	Ide and Wollschlaeger, 1969
Ectrodactyly-ectodermal dysplasia-clefting syndrome	Ectrodactyly (hands and feet), sparse blond hair, oligodontia, nasolacrimal duct obstruction	Common	Autosomal dominant with reduced penetrance, may be etiologically heterogeneous with an autosomal recessive type	Bixler et al., 1971
Freire-Maia syndrome	Tetraperomelia, large deformed ears, sparse hair, hypoplastic nipples, oligodontia, conical crown form, hypogonadism, mental deficiency	Uncommon	Autosomal recessive	Freire-Maia, 1970
Fetal face syndrome	Macrocephaly, ocular hypertelorism, flat nose, overfolding of helix, mesomelia, clinodactyly, vertebral anomalies, genital anomalies	Rare	Etiologically heterogeneous with common autosomal dominant type and rare autosomal recessive type	Cohen, 1977
Gorlin syndrome	Multiple basal cell carcinomas, jaw cysts, skeletal anomalies	Uncommon	Autosomal dominant	Gorlin and Sedano, 1972
Hemifacial microsomia (Goldenhar syndrome)	Unilateral dysplastic ear, ear tags and/or pit, unilateral hypoplasia of mandibular ramus, and variably epibulbar dermoids, vertebral anomalies, cardiac defects, renal anomalies, other abnormalities	Uncommon	Most cases sporadic, few familial instances, pedigrees compatible with autosomal dominant and autosomal recessive transmission	Gorlin et al., 1976
Hypertelorism-hypospadias syndrome	Hypertelorism, hypospadias, other abnormalities	Uncommon	Autosomal dominant with predominantly male sex limitation	Opitz et al., 1969
Juberg-Hayward syndrome	Microcephaly, hypoplastic distally placed thumbs, short radii	Common	Autosomal recessive	Juberg and Hayward, 1969

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TABLE 2—*Continued*

Meckel syndrome	Polydactyly, polycystic kidneys, encephalocele, cardiac anomalies, other abnormalites	Common	Autosomal recessive	Hsia et al., 1971
Oculo-dento-osseous dysplasia	Narrow nose, hypoplastic alae, microcornea, iris anomalies, syndactyly and camptodactyly of fourth and fifth fingers, enamel hypoplasia	Rare	Autosomal dominant	Gorlin et al., 1976
Popliteal pterygium syndrome	Popliteal pterygia, musculoskeletal anomalies especially hypoplastic digits, genitourinary anomalies, other abnormalities	Common	Probably autosomal dominant	Gorlin, et al., 1968.
Pseudothalidomide syndrome	Tetraphocomelia, hypoplastic cartilage of alae and pinnae, facial hemangiomas, mental deficiency	Uncommon	Autosomal recessive	Herrmann et al., 1969a
Rapp-Hodgkin syndrome	Hypohidrosis, thin wiry hair, dystrophic nails	Common	Autosomal dominant	Rapp and Hodgkin, 1968
van der Woude syndrome	Lip pits	Common	Autosomal dominat	Cervenka et al., 1967
Waardenberg syndrome	Dystopia canthorum, synophrys, heterochromia irides, deafness, poliosis, vitiligo	Uncommon	Autosomal dominant	Pantke and Cohen, 1971
Environmentally-Induced Syndromes				
Amniotic band syndrome	Ring constrictions and amputations of digits or limbs, encephalocele, bizarre facial clefts, other abnormalities	Uncommon	Amniotic bands	Jones et al., 1974
Fetal hydantoin syndrome	Digit and nail hypoplasia, unusual facies, growth and psychomotor retardation, other anomalies	Uncommon	Diphenylhydantoin during pregnancy	Hanson and Smith, 1975b
Fetal trimethadione syndrome	Mental deficiency, speech disorder, V-shaped eyebrows, epicanthal folds, low-set ears with overfolded helix, other anomalies	Uncommon	Trimethadione or paramethadione during pregnancy	Zackai et al., 1975
Unknown-Genesis Syndromes				
Clefting/ectropion syndrome	Ocular hypertelorism, ectropion of lower eyelids, digital and/or limb reduction defects	Common	Almost all cases sporadic to date, one known familial instance	Gorlin et al., 1971a
Herrmann syndrome II	Microbrachycephaly, craniosynostosis, symmetrically malformed limbs, mental deficiency	?	? Sporadic to date	Herrmann et al., 1969b
Pilotto syndrome	Growth retardation, mental deficiency, microbrachycephaly, ocular hypertelorism, malformed ears, high nasal bridge, facial asymmetry, short neck, low posterior hairline, patent ductus arteriosus, hypoplastic external genitalia, scoliosis, rib defects, other skeletal anomalies	?	? Sporadic to date	Pilotto et al., 1975
Wildervanck-Smith syndrome	Mandibulofacial dysostosis, upper and lower limb deficiency	?	? Sporadic to date	Bergsma, 1975
Yong syndrome	Undifferentiated myopathy, retinitis pigmentosa, short stature mild developmental delay, seizures	Incomplete cleft lip ?	Sporadic to date	Yong et al., 1977

TABLE 3. Syndromes with cleft palate

syndrome	*striking features*	*relative frequency of cleft palate in syndrome*	*etiology*	*references*
Monogenic Syndromes				
Aase-Smith syndrome	Hydrocephaly, Dandy-Walker malformation, hip dislocation, malformed ears, other malformations	?	? Autosomal dominant	Aase and Smith, 1968
Abruzzo-Erickson syndrome	Coloboma, large soft ears, flat malar region, sensorineural deafness, hypospadias, short stature, other defects	Common	Autosomal dominant vs. X-linked dominant	Abruzzo and Erickson, 1977
Acroosteolysis syndrome	Dissolution of the terminal phalanges with clubbing of fingers, short stature kyphosis, genua valga, midface hypoplasia, micrognathia, dolichocephaly, bathrocephaly, premature loss of teeth	Submucous cleft with bifid uvula uncommon	Autosomal dominant	Weleber and Beals, 1976
Apert syndrome	Craniosynostosis, ocular hypertelorism, downslanting palpebral fissures, proptosis, midface deficiency, symmetric syndactyly of the hands and feet minimally involving digits 2, 3, and 4, mental deficiency	Common	Autosomal dominant	Cohen, 1975
Bencze syndrome	Facial asymmetry, strabismus, amblyopia	Submucous cleft palate common	Autosomal dominant	Bencze et al., 1973; Cohen, 1977
Braun-Bayer syndrome	Urinary tract anomalies, rudimentary distal phalanges with bifid ends, conduction deafness	Cleft uvula only (2/5)	? X-linked or autosomal recessive	Braun and Bayer, 1962
Campomelic syndrome	Flat face, hypertelorism, hypoplastic scapulas, thoracic vertebral defects, bowing of femora and tibiae, pretibial dimpling, valgus deformity of feet, other abnormalites, commonly lethal before six months of age	Common	Autosomal recessive type, etiologically heterogeneous	Opitz et al., 1974
Cerebrocostomandibular syndrome	Microcephaly, posterior rib gap defects, other abnormalities, commonly lethal during neonatal period	Common	Autosomal recessive	Langer and Herrmann, 1974
de la Chapelle syndrome	Micromelic dwarfism, low-set ears, ocular hypertelorism, flat nasal root, short curved bones (especially radius and ulna), triangular fibula and ulna, double phalanges, vertebral anomalies, patent foramen ovale, patent ductus arteriosus, commonly lethal	2/2	Autosomal recessive	de la Chapelle et al., 1972
Chondrodysplasia punctata (rhizomelic type)	Short femora and humeri, prominent forehead, flat face, cataracts, stippled epiphyses, other abnormalities, commonly lethal	Uncommon	Autosomal recessive	Gorlin et al.,1976
Christian syndrome	Craniosynostosis, microcephaly, arthrogryposis, adducted thumbs	Common	Autosomal recessive	Christian et al., 1971
Cleft palate/brachial plexus neuritis syndrome	Recurrent brachial plexus neuritis, limited extension at the elbows, winging of the scapulae, facial asymmetry, down-slanting palpebral fissures, deep-set hypoteloric eyes	Common	Autosomal dominant	Erickson, 1974

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TABLE 3—*Continued*

Cleft palate/connective tissue dysplasia syndrome	Cervical fusions, downslanting palpebral fissures, micrognathia, dislocated radial heads, clinodactyly, positional foot deformities	Submucous cleft palate (2/2)	? X-linked or autosomal recessive	Cohen, 1977
Cleft palate/lateral synechiae syndrome	Lateral synechiae	Common	Autosomal dominant	Fuhrmann et al., 1972
Cleft palate/stapes fixation syndrome	Stapes fixation, hypodontia, skeletal anomalies	2/2	Autosomal recessive	Gorlin et al., 1971b
Cleidocranial dysplasia	Large calvaria, relatively small face, wormian bones, persistent fontanels, supernumerary teeth, delayed eruption or failure of eruption, absent or hypoplastic clavicles, other skeletal abnormalities	Submucous cleft palate common	Autosomal dominant	Gorlin et al., 1976
Davis-Lafer syndrome	Mental deficiency, hypotonia, growth deficiency, frontal bossing, epicanthal folds, other abnormalities	2/2	? Autosomal recessive	Davis and Lafer, 1976
Diastrophic dwarfism	Short stature, contractures, clubfoot, hitch-hiker's thumb, cystic ear, other defects	Common	Autosomal recessive	Walker et al., 1972
Donlan syndrome	Thin skin, eczema, dental hypoplasia, micrognathia, growth failure, pancreatic insufficiency	Common	? Autosomal recessive	Donlan, 1977
Dubowitz syndrome	Growth deficiency, mild mental deficiency, microcephaly, blepharophimosis, micrognathia, eczema	Submucous cleft, bifid uvula common	Autosomal recessive	Gorlin et al., 1976
Eastman syndrome	Horseshoe kidneys, cardiac anomalies, severe mental deficiency, neuromuscular abnormalities, malar hypoplasia, broad nasal root, prominent ears, plagiocephaly, hypodontia	1/3	Autosomal recessive	Eastman and Bixler, 1977
Ectrodactyly-cleft palate syndrome	Ectrodactyly and syndactyly (hands and feet)	Common	Autosomal dominant	Opitz, 1975
Fontaine syndrome	Micrognathia, dysplastic ears, ectrodactyly and syndactyly (feet), mental deficiency in some cases	Submucous cleft with bifid uvula uncommon	Autosomal dominant	Fontaine et al., 1974
Gareis-Smith syndrome	Short stature	Common	Dominant (X-linked?)	Gareis and Smith, 1971
Gordon syndrome	Camptodactyly, clubfoot	Common	Autosomal dominant	Gordon et al., 1969
Katcher-Hall syndrome	Short stature, mental deficiency	Common	? Autosomal recessive	Katcher and Hall, 1975
Larsen syndrome	Multiple dislocations, skeletal defects, flat face	Uncommon	Autosomal recessive and autosomal dominant types	Gorlin et al., 1976

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TABLE 3—*Continued*

syndrome	*striking features*	*relative frequency of cleft palate in syndrome*	*etiology*	*references*
Lowry-Miller syndrome	Persistent truncus arteriosus, abnormal right pulmonary artery, intrauterine death	2/2	Autosomal recessive	Lowry and Miller, 1971
Marden-Walker syndrome	Blepharophimosis, joint contractures, muscular hypotonia, other abnormalities	Uncommon	Autosomal recessive	Marden and Walker, 1966
Marfan syndrome	Dolichostenomelia, arachnodactyly, ectopia lentis, aortic aneurysm	Very uncommon	Autosomal dominant	Gorlin et al., 1976
Megepiphyseal dwarfism	Enlarged joints, abbreviated long bones, large epiphyses, flared metaphyses	?	? Autosomal recessive	Gorlin et al., 1973
Micrognathic dwarfism	Micromelic dwarfism, small mandible, cleft vertebrae	Common	Autosomal recessive	Maroteaux et al., 1970
Multiple pterygia syndrome	Multiple pterygia	Common	Autosomal recessive	Gorlin et al., 1976
Nance-Sweeney chondrodysplasia	Rhizomelic dwarfism, dysplastic ears, thick leathery skin, soft tissue calcifications	?	Autosomal recessive	Nance and Sweeney, 1970
Nager acrofacial dysostosis	Hypoplastic ears, downslanting palpebral fissures, micrognathia, preaxial upper limb deficiency	Uncommon	Autosomal recessive, may be etiologically heterogenesis	Herrmann, 1975
Oral-facial-digital syndrome I	Dystopia canthorum, hypoplastic alar cartilages, milia, multiple frenula, laterally cleft aplate, bifid tongue, malposed teeth, tooth anomalies, brachydactyly, syndactyly, clinodactyly	Common	X-linked dominant, lethal in the male	Gorlin et al., 1976
Oral-facial-digital syndrome II	Lobed tongue, manual polydactyly, bilateral polysyndactyly of the halluces	Uncommon	Autosomal recessive	Gorlin et al., 1976
Otopalatodigital syndrome	Frontal prominence, ocular hypertelorism, broad nasal root, occipital prominence, conduction deafness, short terminal phalanges and short nails on fingers and toes, fifth finger clinodactyly, widely spaced curved toes, dislocation of the radial heads, pectus excavatum	Common	X-linked	Gorlin et al., 1976
Palant syndrome	Microcephaly, short stature, mental deficiency, almond-shaped deep-set eyes, bulbous nasal tip, clinodactyly of toes, prominence of anteromedial aspects of wrists	2/2	Autosomal recessive	Palant et al., 1971
Pena-Shokeir syndrome	Prenatal onset growth deficiency, perinatal death, low-set ears, ocular hypertelorism, epicanthal folds, depressed nasal tip, muscular atrophy, arthrogryposis, clubfeet, camptodactyly	Cleft palate uncommon	? Autosomal recessive	Pena and Shokeir, 1974; Mease et al., 1976

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TABLE 3—*Continued*

Persistent left superior vena cava syndrome	Persistent left superior vena cava, atrial septal defect, clubfoot	Common	X-linked recessive	Gorlin et al., 1970
Phillips-Griffiths syndrome	Growth deficiency, macular colobomas, hallux valgus, flexion deformities of the distal interphalangeal joint of the fifth fingers, other abnormalities	Apparently common	? Autosomal recessive	Phillips and Griffiths, 1969
Pseudodiastrophic dwarfism	Flat nose, ocular hypertelorism, micrognathia, full cheeks, malformed ears, micromelia, talipes equinovarus, externally rotated hands, toe anomalies, other abnormalities	2/2	? Autosomal recessive	Burgio et al., 1974
Rolland syndrome	Short stature, short broad tubular bones with metaphyseal widening, accelerated carpal bone maturation, bowing of legs, as well as thighs and forearms, short broad pelvis with wide flared iliac wings, vertebral anomalies, respiratory distress, micrognathia	2/3	Sporadic. One report suggests affected sibs. Questionable autosomal recessive	Langer et al., 1976
Rudiger syndrome	Growth retardation, flexion contractures of the hands, simian creases, small fingers and fingernails, ureteral stenosis, coarse facies, lethal during first year of life	2/2	Autosomal recessive	Rudiger et al., 1971
Saethre-Chotzen syndrome	Craniosynostosis, facial asymmetry, low-set frontal hairline, ptosis of the eyelids, deviated nasal septum, variable brachydactyly, variable cutaneous syndactyly especially of the 2nd and 3rd fingers.	Rare	Autosomal dominant	Pantke et al., 1975
Saldino-Noonan syndrome	Short-limbed dwarfism, postaxial polydactyly, brachydactyly, narrow thorax, protuberant abdomen, death in utero or shortly after birth, multiple internal malformations especially transposition of the great vessels, hypoplastic lungs, anal atresia, anomalies of the genital organs	Uncommon	Autosomal recessive	Gordon and Brown, 1976
Say syndrome	Small head size, large ears, short stature, tapering fingers, hypoplastic distal phalanges, proximally placed thumbs	Apparently common	Autosomal dominant	Say et al., 1975
Skeletal-apocrine-mammary syndrome	Ulnar ray deficiency involving 4th and 5th fingers, apocrine gland hypoplasia, mammary gland hypoplasia, delayed sexual maturation	Bifid uvula (1/7)	Autosomal dominant vs. X-linked dominant	Pallister et al., 1976
Smith-Lemli-Opitz syndrome	Growth deficiency, mental deficiency, broad nasal tip, anteverted nostrils, ptosis of the eyelids, broad alveolar ridges, micrognathia, hypospadias, cryptorchidism, 2-3 syndactyly of feet	Uncommon	Autosomal recessive	Gorlin et al., 1976
Spondyloepiphyseal dysplasia congenita	Disproportionate short stature involving neck and trunk, myopia, retinal detachment	Common	Autosomal dominant	Spranger and Langer, 1970
Stickler syndrome	Myopia, retinal detachment, flat midface, prominent joints with degenerative joint disease, mild epiphyseal dysplasia, over-tubulation of long bones, other abnormalities	Common	Autosomal dominant	Herrmann and Opitz, 1975

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TABLE 3—*Continued*

syndrome	*striking features*	*relative frequency of cleft palate in syndrome*	*etiology*	*references*
Treacher Collins syndrome	Dysplastic low-set ears, downslanting palpebral fissures, micrognathia	Common	Autosomal dominant	Gorlin et al., 1976
VSR syndrome	Short stature, mesomelic shortness of arms, rhizomelic shortening of lower limbs, scoliosis, joint contractures, prominent zygomas, broad maxilla and mandible	?	Autosomal dominant	Herrmann and Opitz, 1977
W syndrome	Mental deficiency, seizures, frontal prominence, anterior cowlick, ocular hypertelorism, downslanting palpebral fissures, strabismus, broad nasal tip, central notch of upper lip, congenitally absent central incisors, prominent lower facial height, cubitus valgus, subluxation at radio-ulnar joints, camptodactyly, clinodactyly	?	? Autosomal dominant	Pallister et al., 1974
Wallace syndrome	Short limbs, deformed rib cage, hydrocephalus, hypoplastic lungs, congenital heart defects, central notch of upper lip	Common	Autosomal recessive	Wallace et al., 1970
Weaver-Williams syndrome	Mental deficiency, diminished subcutaneous tissue and muscle mass, microcephaly, hypoplastic ears, midface hypoplasia, deep set eyes, small down-turned mouth, malformed teeth, long thin neck, generalized bone hypoplasia, increased tubulation of long bones, delayed osseous maturation, down-sloping ribs, clinodactyly	Common	Autosomal recessive	Weaver and Williams, 1977
Wildervanck syndrome	Cervical fusion, deafness, abducens paralysis	Apparently common	Autosomal dominant	Wildervanck, 1960
Environmentally-Induced Syndromes				
Aminopterin syndrome	Cranial dysplasia, craniosynostosis, micrognathia, clubfoot, hypodactyly	Uncommon	Aminopterin as an abortifacient during the first trimester of pregnancy	Shaw and Steinback, 1968
Fetal alcohol syndrome	Growth deficiency, mental deficiency, microcephaly, narrow palpebral fissures, congenital heart defects, joint anomalies, other abnormalities	Uncommon	Chronic alcoholism during pregnancy	Jones et al., 1973
Thalidomide syndrome	Phocomelia, dysplastic ears, facial hemangioma, atresia of esophagus or duodenum, tetralogy of Fallot, renal agenesis	Rare	Thalidomide during pregnancy	Shepard, 1976
Unknown-Genesis Syndromes				
Beckwith-Wiedemann syndrome	Macroglossia, omphalocele, neonatal hypoglycemia, gigantism, other abnormalities	Rare	Most cases sporadic, few familial instances	Gorlin et al., 1976
Charlie M. syndrome	Ocular hypertelorism, seventh nerve paralysis in some cases, absent or conical incisors, variable limb anomalies from oligodactyly to peromelia	?	Sporadic to date	Gorlin et al., 1976

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TABLE 3—*Continued*

Cleft palate/acanthosis nigricans syndrome	Cutis gyratum, acanthosis nigricans, ocular hypertelorism, neonatal teeth, hypodontia, bifid nipples, hypogonadism	?	Sporadic to date	Beare et al., 1969
Coffin-Siris syndrome	Coarse facies, absent fifth fingernails and toenails, growth deficiency, mental deficiency, other abnormalities	Very uncommon	Most cases sporadic to date, one known instance of affected sibs	Gorlin et al., 1976
Femoral hypoplasia- unusual facies syndrome	Upslanting palpebral fissures, short nose with hypoplastic alar cartilages, long philtrum, short or absent femurs and fibulas, other defects	Common	Sporadic to date	Daentl et al., 1976
Glossopalatine ankylosis syndrome	Glossopalatine ankylosis, micrognathia, hypodontia, variable limb anomalies from oligodactyly to peromelia	Uncommon	All cases sporadic to date	Gorlin et al., 1976
Hausam syndrome	Craniosynostosis, asymmetric craniofacies, ocular proptosis, flat forehead, low-set posterior hairline, contractures at elbows and knees, plantar furrows, absent thumbs, absent middle phalanges (various), imperforate anus, sudden infant death syndrome	2/2	Unknown (MZ twins)	Hausam et al., 1977
Ho syndrome	Micrognathia, wormian bones, congenital heart defect, dislocated hips, absent tibiae, bowed fibulae, preaxial polydactyly (feet), simian creases, ulnar deviation of fingers	?	Sporadic to date	Ho et al., 1975
Klippel-Feil syndrome	Block fusion of cervical vertebrae	Fairly common	Almost all cases sporadic, few familial instances (autosomal recessive)	Gorlin et al., 1976; Gunderson et al., 1967
Kniest syndrome	Disproportionate dwarfism, round face, flat midface, short neck, lordosis, kyphoscoliosis, tibial bowing, progressively enlarged stiff and painful joints, clubfeet, severe myopia, retinal detachment, cataracts, deafness, recurrent respiratory infections	Common	Almost all cases sporadic to date; one known familial instance (autosomal dominant?)	Siggers et al., 1974
de Lange syndrome	Microbrachycephaly, confluent eyebrows, anteverted nostrils, long philtrum, thin lips, growth deficiency, mental deficiency, limb anomalies, other abnormalities	Fairly common	Most cases sporadic, few familial instances	Berg et al., 1970
Lowry-MacLean syndrome	Microcephaly, craniosynostosis, seizures, prominent beaked nose, down-slanting palpebral fissures, proptosis, glaucoma, delayed dental development, atrial septal defect, eventration of the diaphragm, narrow hyperconvex fingernails	?	? Sporadic	Lowry and MacLean, 1977
Majewski syndrome	Short narrow thorax, preaxial and postaxial polydactyly of hands and feet, short tibias, protuberant abdomen, cardiac anomalies, genital anomalies, median cleft lip	Common	All cases sporadic to date	Spranger and Grimm, 1974

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TABLE 3—*Continued*

syndrome	*striking features*	*relative frequency of cleft palate in syndrome*		*etiology*	*references*
	and/or palate, other abnormalities, death from respiratory distress				
Short rib-polydactyly syndrome, Type III	Short broad ribs, marked underossification of all bones except skull base and clavicles, disproportionately small trunk and large head, ocular hypertelorism, flipper-like limbs, polysyndactyly of hands, three blob-shaped toes on each foot, persistent left superior vena cava, hypoplastic kidneys, hypoplastic respiratory tract, bicornaute uterus, absent olfactory tract	1/1		? Sporadic. Only one case known.	Hall et al., 1977
Shprintzen syndrome	Hypotonia, poor fine motor coordination, specific learning disability, ventricular septal defect, long face, flat malar region, synophrys, large nose, retruded mandible, overbite	Submucous cleft common	palate	Most cases sporadic; four familial instances	Shprintzen et al., 1978
Walden syndrome	Short humeri and femora, long radii and tibiae	?		? Sporadic	Walden et al., 1971

occurrence of two or more anomalies in the same patient on a nonrandom basis. The etiology and the phenotypic spectrum of anomalies are not well-defined and need further delineation.

Non-Specificity of Clefting

The syndromes presented in Tables 2 through 7 require several general comments. First, syndromes are composed of a number of malformations, each of which is individually nonspecific. Each malformation may occur as an isolated abnormality; each may also occur as a component part of various syndromes. Because malformations occur with different frequencies in different syndromes, they are facultative rather than obligatory, that is, they may or may not be present in a particular instance of a syndrome in which they are said to occur. For example, although congenital heart defects are common in the Meckel syndrome, in some instances, the heart is normal.

Pathognomonic anomalies for various malformation syndromes are either nonexistent or very rare. Since individual malformations are both nonspecific and facultative, the diagnosis of a syndrome is made from the overall pattern of abnormalities. The more anomalies there are in a syndrome, the easier the condition is to diagnose because, even if some of the features are not expressed, the overall pattern is still discernible. Conversely, the fewer abnormalities there are in a syndrome, the more difficult the condition is to diagnose if some of its features are not expressed. In general, diagnosis of any syndrome in which some of its features are not expressed is more of a problem in a sporadic occurrence than in a familial instance.

Tables 2 through 7 should be interpreted in accordance with the preceding discussion. Thus, some of the phenotypic characteristics listed under "distinct features" may not be present in some cases. Furthermore, many low-frequency anomalies that occur in various syndromes are not listed, although they may be found in the references for each condition. Finally, some syndromes are incompletely delineated at the present time. In these instances, new findings will undoubtedly come to light in the future.

Population Definition of a Syndrome

It is sometimes asked if an occasionally observed abnormality is part of a syndrome or not. How frequently does cleft palate, for example, have to occur in a syndrome to be considered a feature of that syndrome? Since the pathogenesis of many syndromes is obscure, there is no direct way of knowing. However, by using a population definition of a syndrome, it can be determined indirectly. If a given abnormality occurs with greater frequency in the syndrome population than it does as an isolated abnormality in the general population, it should be considered part of the syndrome. This principle commits us to statements such as "orofacial clefting is part of the Down syndrome" because clefting occurs three times more commonly than it does as an isolated defect in the general population. However, orofacial clefting is an extremely uncommon feature of the Down syndrome.

The frequency of clefting in various syndromes is not expressed as a percentage in the tables because ascertainment biases inherent in case reports in the literature tend to make percentage estimates inaccurate and misleading. Generally, in all tables, frequency of clefting is listed as "common," "uncommon," or "rare." "Common" should be interpreted to mean that the frequency of clefting is *at least* 30 per cent or higher. Most frequencies listed as "common" are considerably higher (except in Table 5). When only a few instances of a syndrome have been reported, a number may be given in the frequency column. For example, 2/5 means that clefting occurred in two of the five reported cases. Since there are so few cases known, it is not yet possible to ascertain how common clefting will be in the syndrome.

Syndrome Delineation

To date, many anomalies reported in association with cleft lip and cleft palate are not recognized as constituting syndromes of known genesis. In epidemiologic studies of clefting to date, the frequency with which one or more malformations accompany clefts varies from eight to 50 per cent (Gorlin et al., 1976). Undoubtedly, many new syndromes of known genesis will be delineated from this group in the future. Thus, the estimate of less than three per cent of all cases of clefting being associated with "syndromes" (Fraser, 1970) is too low in our opinion.

The significance of syndrome delineation cannot be overestimated. In a large study of newborn infants with multiple anomalies of all kinds (malformation syndromes), only 40 per cent had known, recognized entities (Marden et al., 1964). The other 60 per cent represented provisionally-unique-pattern syndromes that needed to be further delineated. As an unknown syndrome becomes delineated, its phenotypic spectrum, its natural history, and its inheritance pattern or risk of recurrence become known, allowing for 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 which may produce clinical problems at a later time, such as a hemivertebra in the Goldenhar syndrome. If a certain complication can occur in a given disorder, such as a Wilms tumor in the Beckwith-Wiedemann syndrome, the clinician is forewarned to monitor the patient with intravenous pyelograms. 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. For example, cleft palate or the Robin complex is a common feature of the Stickler syndrome, an autosomal dominant disorder with a 50 per cent recurrence risk when one parent is affected. In this condition, retinal detachment is thought to occur in 20 per cent of reported cases and blindness in 15 per cent (Herrmann et al., 1975). Genetic counseling is of great importance because the risk of development of serious ocular problems is high. This relatively common condition also illustrates the importance of syndrome delineation because the entity was unknown and unrecognized before 1965, although surely it existed before that time. Thus, the overall treatment program gains rationality if a syndrome is delineated. In contrast, with a provisionally-unique-pattern syndrome, the treatment program and overall management frequently leave something to be desired.

TABLE 4. Conditions associated with the Robin complex

condition	*striking features*	*frequency of Robin complex in given condition*	*etiology*	*reference*
Monogenic Syndromes				
Beckwith-Wiedemann syndrome	Macroglossia, omphalocele, visceromegaly, neonatal hypoglycemia, gigantism, other defects	Uncommon, isolated cleft palate uncommon	Most cases sporadic, few familial instances	Cohen et al., 1971
Campomelic syndrome	Flat face, hypertelorism, hypoplastic scapulas, thoracic vertebral defects, bowing of femurs and tibias, pretibial dimpling, valgus deformity of foot, other abnormalities	Common	Autosomal recessive type, etiologically heterogeneous	Storer and Grossman, 1974
Cerebrocostomandibular syndrome	Microcephaly, posterior rib gap defects, other abnormalities	Common	Autosomal recessive	Langer and Herrmann, 1974
Diastrophic dwarfism	Short stature, contractures, clubfoot, hitch-hiker's thumb, cystic ear, other defects	Uncommon, isolated cleft palate common	Autosomal recessive	Hanson and Smith, 1975a; Walker et al., 1972
Donlan syndrome	Thin skin, eczema, dental hypoplasia, micrognathia, growth failure, pancreatic insufficiency	Cleft palate (2/2) Robin complex (1/2)	? Autosomal recessive	Donlan, 1977
Myotonic dystrophy (severe congenital)	Myotonia, progressive muscle wasting, cataracts, various other abnormalities	Uncommon	Autosomal dominant	Opitz, 1975
Persistent left superior vena cava syndrome	Persistent left superior vena cava, atrial septal defect, talipes equinovarus	Common	X-linked recessive	Gorlin et al., 1970[a]
Radiohumeral synostosis syndrome	Radiohumeral synostosis, anosmia	? Too few cases known	? Autosomal dominant	Hanson and Smith, 1975[a]
Spondyloepiphyseal dysplasia congenita	Disporportionate short stature involving neck and trunk, myopia, retinal detachment	Uncommon, isolated cleft palate common	Autosomal dominant	Holthusen, 1972; Spranger and Langer, 1970.
Stickler syndrome	Myopia, retinal detachment, flat midface, prominent joints with degenerative joint disease, mild epiphyseal dysplasia, overtubulation of long bones, other abnormalities	Common; isolated cleft palate common	Autosomal dominant	Herrmann et al., 1975
Chromosomal Syndromes				
Trisomy 11q	Axial hypotonia, limb hypertonia, wrinkled face, beaked nose, low-set malformed ears, short neck, narrow chest, widely spaced nipples, congenital heart defect, renal agenesis, malformations of urinary tract, micropenis, acetabular dysplasia, clubfoot	Micrognathia most common; cleft palate second most common; glossoptosis least common	Trisomy for the distal segment of the long arm of chromosome 11	Aurias and Laurent, 1975

(continued on next page)

TABLE 4—*Continued*

Teratogenically-Induced Syndromes				
Fetal alcohol syndrome	Growth deficiency, mental deficiency, microcephaly, narrow palpebral fissures, congenital heart defects, joint anomalies, other abnormalities	Uncommon	Chronic alcoholism during pregnancy	Jones et al., 1973
Fetal hydantoin syndrome	Digit and nail hypoplasia, unusual faces, growth and psychomotor retardation, other anomalies	Uncommon, cleft lip and palate also observed	Diphenylhydantoin during pregnancy	Hanson and Smith, 1975b
Fetal trimethadione syndrome	Mental deficiency, speech disorders, V-shaped eyebrows, epicanthus, low-set posteriorly rotated ears with overfolded helix, cardiac anomalies, irregular teeth, other defects	Uncommon, cleft lip and palate also observed	Trimethadione during pregnancy	Zackai et al., 1975
Unknown-Genesis Syndromes				
Femoral dysgenesis-unusual facies syndrome	Upslanting palpebral fissures, short nose with hypoplastic alar cartilages, long philtrum, short or absent femurs and fibulas, other defects	Micrognathia and cleft palate common, glossoptosis uncommon	Sporadic, cause unknown	Daentl et al., 1975
Martsolf syndrome	Square forehead, abnormal ears, wide-set eyes, small mouth, mild neck webbing, short neck, rhizomelic brachymelia, broad thumb, short index finger, broad halluces with valgus deformity, postaxial hexadactyly of the feet, skeletal abnormalities	? Too few cases known	Sporadic, cause unknown	Martsolf et al., 1977
Robin-accessory metacarpal syndrome	Bilateral accessory metacarpal of index finger with clinodactyly, pectus carinatum	? Too few cases known	Sporadic, one instance of affected sibs	Holthusen, 1972; Gewitz et al., 1978
Robin-amelia syndrome	Amelia	? Too few cases known	Sporadic, cause unknown	Holthusen, 1972

TABLE 5. Chromosomal syndromes with clefts and palatal anomalies (part I)

*karyotype**	*striking features*	*cleft** lip*	*cleft** palate*	*bifid** uvula*	*references*
1q+	Beaked nose, prominent ears, micrognathia, long tapered fingers, congenital heart defect, involuted or absent thymus	+?	+?	−	Norwood and Hoehn, 1974
3p+	Microbrachycephaly, frontal bossing, high forehead, ocular hypertelorism, epicanthic folds, large mouth, short neck, congenital heart defect	−	++	−	Ballesta and Behi, 1974
3p−,q+	Distorted forehead, low-set ears, upslanting palpebral fissures, short nose, anteverted nostrils, low nasal bridge, micrognathia, omphalocele or umbilical hernia, talipes equinovarus, congenital heart defects, renal anomalies, cryptorchidism, failure to thrive, frequent early demise	+	++	±	Allderdice et al., 1975
4p−	Severe growth and psychomotor retardation, seizures, hypotonia, small head, ocular hypertelorism, prominent glabella, downslanting palpebral fissures, preauricular dimple, short philtrum, downturned mouth, micrognathia, congenital heart defects, cryptorchidism, hypospadias, dimpling at the sacrum	+?	+?	−	Sedano et al., 1971
4q−	Mental deficiency, ocular hypertelorism, superiorly pointed ears, flat nasal bridge, micrognathia, displaced nose, cardiac defects, sacral dimple, limitation of extension at the elbows, skeletal anomalies	+?	+?	−	Van Kempen, 1975
5p−	Cat-like cry during infancy, microcephaly, round face, ocular hypertelorism, downslanting palpebral fissures, strabismus, low-set ears, mild micrognathia, mental deficiency, growth deficiency	±	±	±	Sedano et al., 1971
6q−	Microcephaly; epicanthic folds; large, low-set malformed ears; micrognathia; short neck; congenital heart defect; lip dysplasia; talipes equinovarus; short stature; developmental delay.	−	+?	−	Bartoshesky, et al., 1978
7p−	Craniosynostosis, other variable anomalies, incompletely delineated phenotype	−	−	+?	McPherson et al., 1976
7q+	Low birth weight, mental deficiency, fuzzy hair, wide anterior fontanel, small palpebral fissures, ocular hypertelorism, small nose, large tongue, malformed low-set ears, skeletal anomalies	−	++	−	Vogel et al., 1973
7q−	Prominent forehead, brachycephaly, prominent nose with bulbous tip, myopia, simple cupped ears, prominent labia, anal skin tags, hyperextensible joints, relatively lax skin	−	+?	−	Harris et al., 1977
10p+	Ocular hypertelorism, low-set malformed ears, micrognathia, pes varus, anal atresia, rectovaginal fistula, absent lung lobe, incompletely delineated phenotype	+?	+?	−	Nakogome and Kobayashi, 1975
10q+	Growth deficiency, psychomotor retardation, microcephaly, flat rounded face, arched eyebrows, narrow palpebral fissures, microphthalmia, malformed ears, small nose, micrognathia, short neck, proximally placed thumbs and great toes, overlapping fingers, soft tissue syndactyly, camptodactyly, deep plantar furrows, reduced renal function	−	++	−	Yunis and Sanchez, 1974
11p+	Mental deficiency, hypotonia, frontal bossing, downslanting palpebral fissures, strabismus, nystagmus, broad fingers and toes	−	++	−	Sanchez et al., 1974

(continued on next page)

TABLE 5—*Continued*

11q+	Axial hypotonia, limb hypertonia, wrinkled face, large beaked nose, micrognathia, malformed low-set ears, short neck, narrow chest, widely spaced nipples, micropenis, renal agenesis, urinary tract malformations, acetabular dysplasia, clubfoot, congenital heart defects, genital anomalies	−	++	−	Aurlas and Laurent, 1975
13+	Holoprosencephaly, seizures, apneic episodes, severe mental deficiency, early demise, severe facial dysmorphia (including ocular hypotelorism, flat nose, microphthalmia), iris coloboma, malformed ears, glabellar hemangioma, scalp defects, polydactyly, congenital heart defects, genital anomalies	++	++	−	Smith, 1969
13q+^{p}	Psychomotor retardation, low-set ears, clinodactyly, simian creases, microphthalmia, iris coloboma	−	+	−	Escobar and Yunis, 1974
13q−	Microcephaly, lobar holoprosencephaly, trigonocephaly, mental deficiency, microphthalmia, iris coloboma, retinoblastoma, malformed ears, micrognathia, hypoplastic thumbs, imperforate anus, hypospadias, cryptochidism, congenital heart defects	−	+	±	Orbeli et al., 1971
14q+	Mental deficiency, failure to thrive, seizures, microcephaly, microphthalmia, flat nasal bridge, low-set or malformed ears, micrognathia, cryptorchidism	−	++	−	Short et al., 1972; Muldal et al., 1973
18+	Prominent occiput, narrow bifrontal diameter, low-set malformed ears, micrognathia, growth deficiency, mental deficiency, hypertonicity, overlapping fingers, congenital heart defects, early demise	+	+	−	Smith, 1969
18p−	Mental deficiency, failure to thrive, epicanthic folds, ptosis, ocular hypertelorism, micrognathia, short neck, variable phenotype from Turner-like features to holoprosencephaly with facial dysmorphia	+	+	−	de Grouchy, 1969; Lurie and Lazjuk, 1972
18q−	Short stature, microcephaly, mental deficiency, midface hypoplasia, deep-set eyes, prominent antihelix, carp-shaped mouth, tapering fingers, increased digital whorls, congenital heart defects	+	+	−	Lurie and Lazjuk, 1972; Lejeune et al., 1968

Key

* Nos. 1 through 22 = chromosome no.
p = short arm
q = long arm
+, = following no. or letter = trisomy or deletion of chromosome or chromosome segment
13q+^{p} = partial trisomy for the proximal part of the long arm of chromosome 13
Boldface = more well-known chromosomal syndromes or most common chromosomal syndromes or both

**
− = absent or not reported to date
± = rare
+? = reported but relative frequency unknown since syndrome is incompletely delineated
+ = uncommon
++ = common (>15%)

(continued on next page)

TABLE 5—*Continued*

*karyotype**	*striking features*	*cleft** *lip*	*cleft** *palate*	*bifid** *uvula*	*references*
21+	Brachycephaly, flat midface, upslanting palpebral fissures, Brushfield spots, epicanthic folds, small malformed ears, protruding tongue, loose skin on posterior neck, delayed dentition, minor tooth anomalies, malocclusion, periodontal disease, brachydactyly, clinodactyly, simian creases, increased ulnar loops, congenital heart defects, hypotonia, hyperflexibility, short stature, mental deficiency	±	±	−	Cohen and Cohen, 1971
21q−	Psychomotor and mental deficiency, hypertonia, growth deficiency, microcephaly, downslanting palpebral fissures, broad nasal root, prominent low-set ears, large external auditory canals, micrognathia, hypospadias, cryptorchidism, inguinal hernia, pyloric stenosis, skeletal anomalies	+?	+ +	−	Gorlin et al., 1976
22+	Growth deficiency, mental deficiency, hypotonia, underdeveloped musculature, microcephaly, craniofacial asymmetry, long beaked nose, long philtrum, micrognathia, large low-set malformed ears, preauricular tags and pits, strabismus, long slender fingers, finger-like thumbs, congenital heart defects, hip dislocation, cryptochidism	−	+ +	−	Penchaszadeh and Coco, 1975
22q+	Psychomotor retardation, colomboma of iris and choroid, downslanting palpebral fissures, ocular hypertelorism, preauricular tags or pits, anal atresia, rectovaginal fistula, cardiac, genitourinary, and skeletal anomalies	−	+?	−	Bühler et al., 1972
22q−	Mental deficiency, hypotonia, epicanthic folds, flat nasal bridge, soft tissue syndactyly of second and third toes, clinodactyly of fifth fingers	−	−	+ +	DeCicco et al., 1973
X0	Short stature, ovarian agenesis, infantile vagina and breasts, widely-spaced nipples, webbed neck, low posterior hairline, prominent ears, micrognathia, cubitus valgus, short fourth metacarpals, peripheral lymphedema during infancy, coarctation of the aorta, renal anomalies, hypoplastic nails, multiple pigmented nevi	−	±	−	Gorlin et al., 1976
XXXXY	Mild microcephaly, severe mental deficiency, hypotonia, upslanting palpebral fissures, ocular hypertelorism, epicanthic folds, short neck, redundant posterior neck skin, taurodontism, mandibular prognathism, micropenis, small testes, cryptorchidism, radioulnar synostosis, cubitus valgus, genua valga	−	+	−	Gorlin et al., 1976
Triploidy	Growth deficiency, mental deficiency, hypotonia, asymmetry, microphthalmia, iris and choroid colobomas, mild ocular hypertelorism, anomalous low-set ears, micrognathia, syndactyly of the third and fourth fingers, simian creases, clubfoot, congenital heart defects, genital anomalies	+ +	+ +	−	Gorlin et al., 1976

TABLE 6. Conditions with median cleft lip

conditions	*striking features*	*relative frequency of median cleft lip in condition*	*etiology*	*references*
Frontonasal dysplasia	Ocular hypertelorism, widow's peak, anterior cranium bifidum occultum, wide-set nostrils, lack of elevation of the nasal tip, notching or colobomas of nostrils, other abnormalities	Uncommon	Most cases sporadic, few familial instances, probably etiologically heterogeneous	Gorlin et al., 1976
Majewski syndrome	Short narrow thorax, preaxial and postaxial polydactyly of hands and feet, short tibias, protuberant abdomen, cardiac anomalies, genital anomalies, cleft lip and/or palate, other abnormalities, death from respiratory distress	Common	All cases sporadic to date	Spranger et al., 1974
Oral-facial-digital syndrome I	Dystopia canthorum, hypoplastic alar cartilages, milia, multiple frenula, laterally cleft palate, bifid tongue, malposed teeth, tooth anomalies, brachydactyly, syndactyly, clinodactyly	Common	X-linked dominant, lethal in the male	Gorlin et al., 1976
Oral-facial-digital syndrome II	Lobed tongue, manual polydactyly, bilateral polysyndactyly of halluces	Common	Autosomal recessive	Gorlin et al., 1976
Premaxillary agenesis	Median cleft lip, flat nose, ocular hypotelorism, holoprosencephaly, other abnormalities, amentia, seizures, apnea, neonatal demise	Common	Etiologically heterogeneous (trisomy 13 syndrome, 18p- karyotype, other chromosomal aberrations, Meckel syndrome, autosomal recessive, autosomal dominant with markedly variable expressivity)	Cohen and Hohl, in press
W syndrome	Mental deficiency, seizures, frontal prominence, anterior cowlick, ocular hypertelorism, downslanting palpebral fissures, strabismus, broad nasal tip, central notch of upper lip and submucous cleft palate, congenitally absent central incisors, prominent lower facial height, cubitus valgus, subluxation at radioulnar joints, camptodactyly, clinodactyly	?	? Autosomal dominant	Pallister et al., 1974
Wallace syndrome	Short limbs, deformed rib cage, hydrocephalus, hypoplastic lungs, congenital heart defects, central notch of upper lip and cleft palate	Common	Autosomal recessive	Wallace et al., 1970

TABLE 7. Association of clefts with other abnormalities

type of cleft	*association*	*comment*	*references*
Cleft lip or cleft palate or both	Thoracopagus twins		Gorlin et al., 1971a
Cleft palate	Oral duplication		Gorlin et al., 1971a
Cleft lip or cleft palate or both	Anencephaly		Gorlin et al., 1971a
Cleft palate	Congenital oral teratoma	Cleft palate probably secondary to teratoma	Gorlin et al., 1971a
Cleft lip or cleft palate or both	Nasal glioma or meningoencephalocele	Cleft palate probably secondary to glioma or meningoencephalocele	Gorlin et al., 1971a
Cleft lip or cleft palate or both	Congenital neuroblastoma	Other associated anomalies frequent	Gorlin et al., 1971a
Cleft lip or cleft palate or both or Robin complex	Congenital cardiovascular defects (ASD, VSD, PDA, pulmonary valvular atresia, tetralogy of Fallot, tricuspid stenosis, coarctation of the aorta, biventricular aorta, cor triloculare, dextrocardia)		Shah et al, 1970; Gorlin et al., 1976
Cleft lip or cleft palate or both	Forearm bone aplasia	Other associated anomalies frequent	Gorlin et al., 1971a
Cleft lip-cleft palate	Sacral agenesis		Gorlin et al., 1971a
Cleft lip-cleft palate	Cleft larynx		Gorlin et al., 1971a
Cleft lip-cleft palate	Laryngeal web		Gorlin et al., 1971a
Cleft lip-cleft palate	Lateral proboscis	Usually occurs with absent nostril on ipsilateral side	Gorlin et al., 1971a
Cleft palate	Persistent buccopharyngeal membrane		Gorlin et al., 1971a
Cleft palate	Aniridia		Gorlin et al., 1971a
Cleft palate	Aplasia of trochlea		Gorlin et al., 1971a

A major task in clinical genetics is to delineate the unknown-genesis syndromes as rapidly as possible. Any clinician may be the first to see and identify a patient with a new malformation syndrome in which orofacial clefting is a feature. As we pointed out earlier, more than half of all malformation syndromes are not recognized as known entities at the present time. The discovery of a new malformation syndrome is equivalent to discovering a new disease. Careful evaluation of the overall pattern of abnormalities (including minor as well as major anomalies) is required. Photographic documentation of the clinical and radiologic findings is essential, especially when subtle phenotypic features defy verbal description. A thorough study of various relatives and an extended pedigree are necessary.

Ideally, the findings of such syndromes should always be published. In practice, familial instances or two or more sporadic instances of a new syndrome are usually published. Provisionally-unique-pattern syndromes are commonly filed away and not published since their significance is uncertain. However, the publication of a distinctive provisionally-unique-pattern syndrome is like an advertisement with a red flag; it reaches a large audience and allows a few clinicians to react by publishing similar cases. When this happens, the syndrome delineation process is underway.

Pathogenesis of Clefting

Finally, we should be careful not to confuse the process of syndrome delineation with our

understanding or lack of understanding of a syndrome's pathogenesis, even at the higher stages of delineation. For example, in a syndrome of known genesis such as the recessively inherited Meckel syndrome, we know nothing about how the homozygous state of the Meckel gene produces such diverse features as encephalocele, polydactyly, polycystic kidneys, and orofacial clefting. Clearly, since so much *etiologic heterogeneity* is known to occur in human syndromes with orofacial clefting, we should expect some *pathogenetic heterogeneity* in the production of clefts as well. A great deal about the pathogenesis of orofacial clefting remains to be learned.

Since this manuscript went to press, Centervold (1978) has called my attention to some new chromosomal syndromes with orofacial clefting. Cleft palate has been observed in the 5-q-syndrome and cleft lip-palate in the 1-q-syndrome.

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