Evaluation and Diagnosis of the Dysmorphic Infant

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KEYWORDS

• Aplasia cutis congenita • Holoprosencephaly • Asymmetric crying facies
• Preauricular tags • Cleft lip with or without cleft palate • Congenital heart defects
• Ventral wall defects • Polydactyly

KEY POINTS

- Congenital anomalies are a significant cause of neonatal intensive care unit (NICU) admissions.
- Congenital anomalies may be genetic in etiology or may be the result of teratogenic exposure or multifactorial inheritance (the interaction of both genetic and environmental factors).
- The presence of a particular congenital anomaly may necessitate evaluation for the presence of other specific associated anomalies or genetic syndromes.
- Most genetic syndromes are defined by a specific pattern of congenital anomalies.
- Some congenital anomalies may be inherited within families as an isolated trait, highlighting the importance of taking a family history and of examining parents for similar anomalies, when appropriate.

INTRODUCTION

Congenital anomalies are present in at least 10% of all NICU admissions, many of whom have an underlying genetic condition.[1] Neonatologists are often the first physicians to evaluate these infants and consequently need to be familiar with various physical differences to pursue further screening for occult malformations, perform diagnostic testing, and appropriately counsel families. The purpose of this article is review the dysmorphology examination with particular attention to anomalies that are readily apparent in the neonatal period.

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An anomaly is a structural defect that deviates from the normal standard and can be categorized as major or minor. A major anomaly has surgical, medical, or cosmetic importance and may be a marker for other occult malformations. A minor anomaly has no significant surgical or cosmetic importance; however, many genetic syndromes are recognized based on the pattern of minor anomalies present. Anomalies arise from 1 of 3 mechanisms, each of which has different diagnostic and inheritance implications. The first mechanism is termed a malformation, which is a structural defect arising from an intrinsically abnormal developmental process. Malformations include anomalies like congenital heart defects and cleft lip and palate. These types of anomalies are more likely associated with a genetic condition or predisposition. A deformation is an abnormality arising from prenatal mechanical forces on otherwise normally formed fetal structures. Deformations can include clubfeet, overlapping toes, and unusual head shape (although these disorders may also be malformations). Deformations are rarely genetic and recurrence risks are typically low. Lastly, disruptions are structural defects resulting from the destruction or interruption of intrinsically normal tissue. Examples of disruptive anomalies include limb reduction defects from amniotic band sequence and certain types of intestinal atresias due to vascular insufficiency.[2] Anomalies due to this mechanism are much less likely due to a genetic condition or to recur in a future pregnancy.

BIRTH PARAMETERS

Both increased and decreased birth parameters are associated with multiple genetic and nongenetic etiologies. Fetal macrosomia may be defined as a birth weight greater than 4000 g or more than 2 SDs above the mean of a reference population, whereas fetal-growth restriction is defined as a birth weight less than 2 SDs below the mean for gestational age in a reference population. The differential diagnoses for both fetal macrosomia and fetal growth restriction are broad and include chromosomal abnormalities and teratogenic exposures. Chromosomal abnormalities have varying phenotypes depending on the size of the chromosomal segment involved and the individual genes in that segment. Consequently, it is beneficial to evaluate for congenital anomalies in those who have macrosomia or growth restriction. In both instances, a chromosomal microarray should be considered. If the physical examination indicates features of a well-characterized genetic syndrome, such as a trisomy or Beckwith-Wiedemann syndrome, then testing can be tailored to that particular syndrome (**Tables 1** and **2**).[3–8]

Although abnormal birth parameters in the presence of congenital anomalies frequently indicate a genetic syndrome, this is not always the case. For example, infants of diabetic mothers are commonly macrosomic (although growth restriction can also occur) and may display congenital malformations at a frequency of 2 to 4 times the general population rate. Consequently, it may be difficult to distinguish between diabetic embryopathy and a genetic syndrome.[4] In the absence of confirmed maternal diabetes and one of the more specific anomalies seen in diabetic embryopathy, such as caudal regression syndrome or tibial hemimelia with preaxial polydactyly (**Fig. 1**), this diagnosis should be considered a diagnosis of exclusion and the clinician should consider further genetic testing, such as a chromosomal microarray, to evaluate for a chromosome abnormality.[2,3]

Similarly, fetal growth restriction can be due to nongenetic causes, such as placental insufficiency, maternal hypertension, multiple gestation (ie, twinning), and maternal preeclampsia. Most of these conditions result in asymmetric growth restriction as a result of inadequate nutrient transfer to the fetus.[9] Placental insufficiency has also been associated with an increased risk of hypospadias in male infants[10]; therefore, not all birth

Table 1
Overgrowth in the neonatal period and associated conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Beckwith-Wiedemann syndrome	Macroglossia Abdominal wall defects Hemihyperplasia Neonatal hypoglycemia Visceromegaly Posterior helical ear pits Anterior linear ear lobe creases	Blood glucose level monitoring Abdominal ultrasound α-Fetoprotein level	Methylation analysis of 11p15
Chromosomal abnormalities	Congenital heart defects Ophthalmologic abnormalities Genitourinary abnormalities	Echocardiogram Ophthalmologic evaluation Renal ultrasound	Chromosomal microarray
Infant of a diabetic mother	HPE Spina bifida Congenital heart defects Neonatal small left colon Vertebral defects Tibial hemimelia with preaxial polydactyly Caudal regression syndrome	Cranial ultrasound or head MRI Echocardiogram Renal ultrasound Sacral ultrasound AP and lateral radiographs of the entire spine	None

Abbreviation: AP, anterior-posterior.

defects associated with growth restriction are genetic. As with diabetic embryopathy, however, this type of teratogenic mechanism should remain a diagnosis of exclusion and chromosomal microarray in such infants should be considered.

APLASIA CUTIS CONGENITA

Aplasia cutis congenita (ACC) is congenital absence of the skin. Although ACC can occur on any part of the body, it most commonly affects the scalp (70%–80% of

Table 2
Fetal growth restriction and associated genetic conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Chromosomal abnormalities	(See Table 1)	(See Table 1)	(See Table 1)
Trisomy 13	HPE Microphthalmia/colobomas Congenital heart defects Cutis aplasia	Head ultrasound Ophthalmologic evaluation Echocardiogram Renal ultrasound	Routine chromosome analysis
Trisomy 18	Prominent occiput Micrognathia Congenital heart defects Horseshoe kidney Overlapping fingers	Echocardiogram Renal ultrasound	Routine chromosome analysis

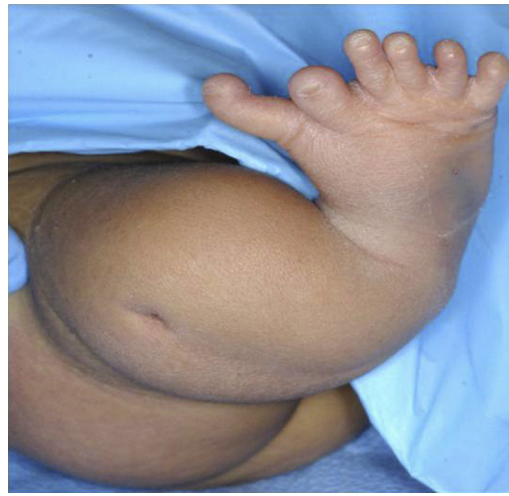

Fig. 1. Tibial hemimelia with proximally placed preaxial polydactyly of the right foot in an infant born to a women with poorly controlled insulin-dependent diabetes. Note the short and bowed lower extremity with a dimple around the knee. (*From* Adam MP, Hudgins L, Carey JC, et al. Preaxial hallucal polydactyly as a marker for diabetic embryopathy. Birth Defects Res A Clin Mol Teratol 2009;85:14; with permission.)

cases). A majority of cases are sporadic solitary scalp lesions but 15% to 30% of scalp ACC cases are associated with defects in the underlying bone and dura.[11] ACC may be associated with etiologic factors, including birth trauma, intrauterine infections with varicella zoster or herpes viruses, fetus papyraceous, and teratogens, like cocaine and methimazole.[11,12] ACC has also been associated with multiple genetic conditions, including trisomy 13 and Adams-Oliver syndrome (AOS), a condition characterized by ACC and terminal limb defects. AOS can be inherited in either an autosomal dominant or an autosomal recessive fashion (**Table 3**).[7,11,13] Complications of ACC include

Table 3
Aplasia cutis congenita and associated genetic conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
AOS	Limb defects Cutis marmorata telangiectasia congenita CNS abnormalities Cardiovascular abnormalities	Brain imaging Limb radiographs Echocardiogram	Sequencing of *ARHGAP31, DOCK6, RBPJ, EOGT*
Scalp or midline back ACC (without multiple anomalies)	May have underlying bony or neural tube defects	Infectious work-up Skull radiograph Head MRI Spinal ultrasound or MRI	None
Trisomy 13	(See Table 2)	(See Table 2)	(See Table 2)

Abbreviation: CNS, central nervous system.

infection, meningitis, bleeding, and superior sagittal sinus thrombosis. Mortality for those with ACC is 20% to 50% and depends on the size of the lesion and any associated defects. Solitary scalp ACC that is small in size and lateral to the midline usually does not require further diagnostic evaluation per se; however, if a scalp or back defect is midline or membranous in quality, a brain MRI or a spine ultrasound or MRI to evaluate for an underlying neural tube defect should be considered. Treatment of ACC is usually conservative.[11] After healing, areas of scalp affected by ACC do not grow any hair (**Fig. 2**).

HOLOPROSENCEPHALY

Holoprosencephaly (HPE) is a structural brain abnormality resulting from the incomplete cleavage of the forebrain into the right and left hemispheres during the third to fourth week of gestation. HPE consists of a continuum of brain malformations with alobar HPE (a single ventricle and no separation of the cerebral hemispheres [**Fig. 3**A]) at one end of the spectrum to very mild midbrain fusion (see **Fig. 3**B) at the other end of the spectrum.

HPE may be associated with a range of craniofacial abnormalities, including cyclopia, microcephaly, hypotelorism, depressed nasal bridge, single maxillary incisor, and midline cleft lip with or without cleft palate (CLP) (**Fig. 4**). Some affected individuals also have pituitary dysfunction and feeding difficulties. The HPE phenotype is variable among simplex cases and among members of the same family with an inherited form of HPE; consequently, subtle facial features may be overlooked in mildly affected family members. In any infant for whom HPE is considered, first-degree relatives should be questioned and examined to identify those with microcephaly, hypotelorism, or a single central incisor. Due to variable expressivity of the phenotype, affected first-degree family members may be mildly affected. Because some cases of HPE are inherited in an autosomal dominant fashion, identifying other affected family members has implications for genetic testing and recurrence risks.[14,15]

The etiologies for both syndromic and nonsyndromic HPE are heterogeneous and include maternal diabetes mellitus, single gene disorders (often inherited in an autosomal dominant manner), and chromosomal abnormalities (**Table 4**).[3,7,16] Chromosomal abnormalities are present in up to 50% of patients with HPE and include trisomy 13, trisomy 18, and a variety of other copy number variants. Determining which laboratory testing to perform depends on family history and the presence of other

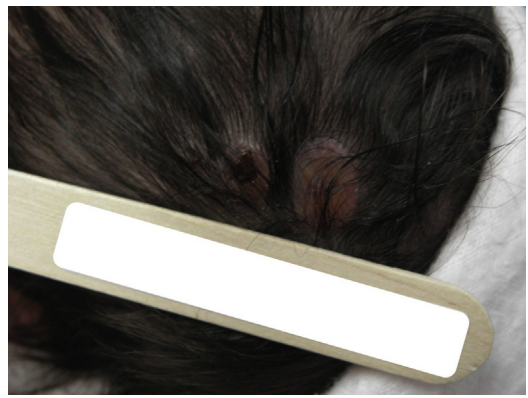

Fig. 2. ACC on the vertex of the scalp. (*Courtesy of* Heather Brandling-Bennett, MD, Seatle, WA.)

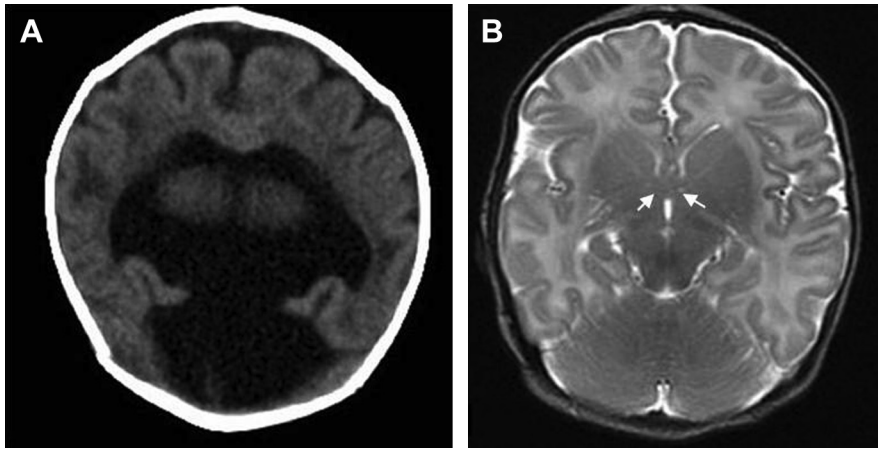

Fig. 3. (*A*) Brain MRI of an infant with alobar HPE, the most severe form of HPE, demonstrating a single large ventricle. (*B*) Brain MRI of an infant with a milder form of HPE in which there is subtle fusion of the thalami (*arrows*).

abnormalities. Testing may include routine chromosome analysis (if trisomy 13 or 18 is suspected) or chromosomal microarray analysis. Further single gene testing may be considered in those with a family history suggestive of an inherited form of HPE, with mutations in *SHH* accounting for up to 30% to 40% of familial cases.[16] Treatment is multidisciplinary and may include pituitary hormone replacement, antiepileptic medications, and surgical repair of midline CLP in those who are more mildly affected.[15]

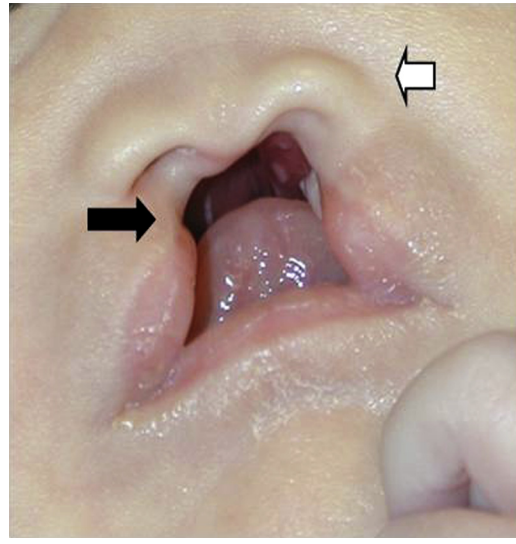

Fig. 4. This infant with HPE has microcephaly, hypotelorism, a hypoplastic nose, and a midline cleft of the lip and palate. The white arrow points to hypoplastic nares and the black arrow points to the large midline cleft lip and palate.

Table 4
Holoprosencephaly and associated conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Chromosomal abnormalities	(See Table 1)	(See Table 1)	(See Table 1)
Infant of diabetic mother	(See Table 1)	(See Table 1)	(See Table 1)
Single gene disorder	Microcephaly Hypotelorism Nasal hypoplasia Midline CLP Single central incisor	Head MRI imaging Dental evaluation in those where teeth have erupted	Sequencing of *SHH, ZIC2, SIX3, TGIF1, GLI2, PTCH*
Trisomy 13	(See Table 2)	(See Table 2)	(See Table 2)
Trisomy 18	(See Table 2)	(See Table 2)	(See Table 2)

ASYMMETRIC CRYING FACIES

Aysmmetric crying facies (ACF) is a minor anomaly, which presents with drooping of the corner of the mouth on the unaffected side when crying or grimacing. Asymmetric crying facies is typically due to congenital absence of the depressor anguli oris muscle (DAOM). Individuals with ACF have preservation of the nasolabial fold depth bilaterally and retain the ability to wrinkle the forehead and to close both eyes equally well, all of which distinguishes this anomaly from the less common facial nerve palsy.[2] ACF has been associated with other congenital anomalies in 20% to 70% of cases. Most anomalies are found in the head/neck and cardiovascular systems but they can also involve the skeletal, genitourinary, and gastrointestinal systems. In particular, ACF has been associated with the 22q11 deletion syndrome (also known as velocardiofacial or DiGeorge syndrome); consequently, individuals with ACF should be evaluated for signs of velocardiofacial syndrome, including dysmorphic facial features, congenital heart defects, and long fingers/toes. Long-term follow-up should focus on evaluation of growth and development and standard treatment of associated anomalies, if present (**Table 5**).[17,18]

Table 5
Asymmetric crying facies and associated conditions

Syndromes/ Conditions to Consider	Associated Features	Potential Evaluations	Potential Genetic Studies
Isolated congenital absence or hypoplasia of DAOM	Congenital heart defects	Echocardiogram	None
22q11 Deletion	Laterally built-up nose Aplasia/hypoplasia of thymus Hypocalcemia Congenital heart defects Long fingers and toes Renal anomalies	Ionized calcium and intact parathyroid hormone levels Thyroid function tests Immunology evaluation Echocardiogram Hearing screen Renal ultrasound Ophthalmologic evaluation	Chromosomal microarray or FISH for 22q11 deletion

PREAURICULAR EAR TAGS AND PITS

Preauricular ear tags and pits are frequent findings on routine neonatal physical examinations. Preauricular tags are small, skin-colored nodules that can be found anywhere along a line drawn from the tragus to the angle of the mouth (Fig. 5). Preauricular pits are small openings at the anterior margin of the crus of the helix. Both of these anomalies can be found in isolation or as part of a genetic syndrome. All patients with a preauricular tag or pit should have a hearing assessment because abnormalities of the external ear may be associated with middle or inner ear abnormalities and hearing loss. Furthermore, these patients should be examined for any other malformations, which may indicate an underlying genetic syndrome like craniofacial microsomia or branchio-oto-renal syndrome (Tables 6 and 7).[2,19,20] The association of preauricular ear tags and pits with urinary tract anomalies has also been studied previously.[20,21] Wang and colleagues[21] suggested renal ultrasound only when ear tags or pits are associated with other malformations or dysmorphic features or if there is a family history of hearing loss, ear anomalies, or maternal gestational diabetes or teratogen exposure. In the absence of these findings, the preauricular tags and pits are presumed isolated and no further evaluation is needed.

OROFACIAL CLEFTING

Orofacial clefts, including CLP and cleft palate only (CP), are the most common craniofacial birth defects in humans, with an incidence of 1 in 700 to 1 in 1000 live births. Subclinical phenotypes may occur and include microform clefts, bifid uvula, submucous CP, and velopharyngeal insufficiency. Most orofacial clefts occur in

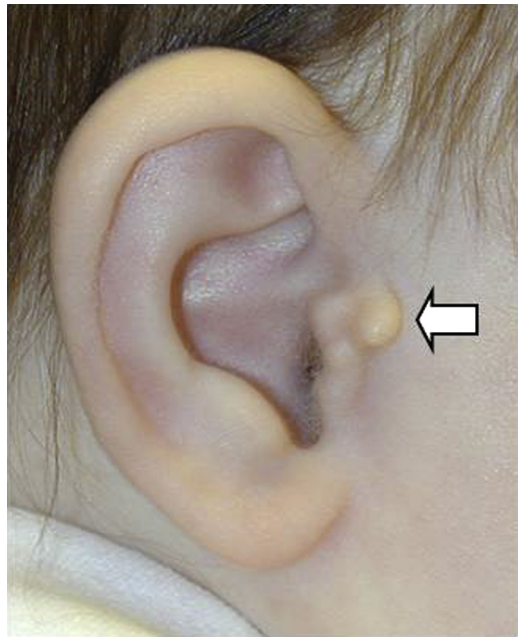

Fig. 5. Arrow pointing to small isolated right preauricular skin tag. (*From* Adam M, Hudgins L. The importance of minor anomalies in the evaluation of the newborn. NeoReviews 2003;4:e99–104.)

Table 6
Conditions associated with preauricular ear tags

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Craniofacial microsomia	External ear anomalies Hearing loss Cleft palate Maxillary and/or mandibular hypoplasia Renal anomalies	Audiology evaluation Renal ultrasound	Chromosomal microarray
Isolated	May have a positive family history	Audiology evaluation	None

isolation, presumably due to the combined effect of genetic and environmental factors. Approximately 30% of CLP and 50% of CP are associated, however, with other malformations, most commonly cerebral, dental, and cardiovascular anomalies.[22] The risk of associated anomalies is even higher in the presence of bilateral clefts. Hearing loss also commonly occurs. The constellation of anomalies may indicate an underlying genetic syndrome, which may require further evaluation (**Tables 8** and **9**).[7,15,18,23–27]

The management of a neonate with an orofacial cleft is multidisciplinary with priority given to respiratory and nutritional support. The cleft itself is treated with orthodontic and surgical interventions. Other services, such as speech therapy, and interventions may be required depending on the clinical presentation (see article by Robin and Hamm elsewhere in this issue for a more detailed discussion).[27]

CARDIAC DEFECTS

Congenital heart disease (CHD) is the most common major congenital anomaly seen by neonatologists and a major cause of neonatal morbidity and mortality. There are multiple etiologies for CHD. Isolated CHD is thought to be the result of multifactorial inheritance with both genetic and environmental factors contributing to the malformation. Other CHDs are due to teratogenic effects of infections (eg, rubella and influenza), maternal factors (eg, diabetes mellitus and phenylketonuria), and prenatal exposures (eg, anticonvulsants and alcohol).[3,28,29]

Genetic etiologies are significant causes of CHD and include trisomies; 45,X (Turner syndrome); chromosomal deletions and/or duplications; and single gene disorders. Although no single cardiac defect is pathognomonic for a particular genetic syndrome, there are certain cardiac defects that are more prevalent in specific syndromes. For example, the 22q11 deletion is present in approximately 50% to 90% of neonates

Table 7
Conditions associated with preauricular ear pits

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Branchio-oto-renal syndrome	External ear anomalies Brachial cleft fistulae Renal anomalies	Audiology evaluation Renal ultrasound	Sequencing of *EYA1, SIX5, SIX1*
Craniofacial microsomia	(See **Table 6**)	(See **Table 6**)	(See **Table 6**)

Table 8
Cleft palate with or without cleft lip associated genetic conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
HPE (if cleft is midline)	(See Table 4)	(See Table 4)	(See Table 4)
Isolated cleft lip/palate	None	Audiology evaluation Feeding assessment	None
Trisomy 13	(See Table 2)	(See Table 2)	(See Table 2)
Van der Woude	Lower lip pits	Feeding assessment	Sequencing of *IRF6*

with an interrupted aortic arch but it is also present in neonates with tetralogy of Fallot, truncus arterious, and ventricular septal defects. Furthermore, many of the patients with CHD and an underlying genetic syndrome have other associated features that help guide further evaluation and testing (**Table 10**).[18,29–33]

Table 9
Cleft palate without cleft lip and associated conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
22q11 Deletion	(See Table 5)	(See Table 5)	(See Table 5)
CHARGE	Coloboma Ear anomalies Cardiac defects Choanal atresia Genitourinary abnormalities Omphalocele	Audiology evaluation ENT evaluation Echocardiogram Ophthalmologic evaluation Renal ultrasound	Sequencing of *CHD7*
Isolated cleft palate	None	None	None
Smith-Lemli-Optiz	Microcephaly Characteristic facial features Cataracts Hypospadias Postaxial polydactyly 2–3 Toe syndactyly	7-Dehydrocholesterol and total cholesterol levels Echocardiogram Ophthalmologic evaluation	Sequencing *DHCR7*
Stickler	Myopia Cataract Retinal detachment Hearing loss Spondyloephiphyseal dysplasia	Audiology evaluation Ophthalmologic evaluation	Sequencing of *COL2A1, COL9A1, COL9A2, COL11A1,* and *COL11A2*
Treacher-Collins	Lower eyelid abnormalities Microtia and other external ear abnormalities Zygomatic bone hypoplasia	Airway and feeding evaluations Audiology evaluation	Sequencing of *TCOF1, POLR1C,* and *POLR1D*

Abbreviation: ENT, ear, nose, and throat.

ESOPHAGEAL ATRESIA/TRACHEOESOPHAGEAL FISTULA

Esophageal atresia (EA) is a developmental defect of the foregut characterized by the discontinuity of the esophagus. It is frequently associated with a tracheoesophageal fistula (TEF) and in approximately half of affected individuals, the EA/TEF anomalies are associated with other congenital anomalies.[34,35] There is a broad spectrum of anomalies associated with EA/TEF, including microcephaly, single umbilical artery, and duodenal atresia. Vertebral, anorectal, cardiac, and genitourinary anomalies are some of the most frequent and are a part of the VACTERL association. VACTERL (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies and Limb abnormalities) association is considered when at least 3 features of the association are present. The genetic etiology of VACTERL has not been elucidated and it is thought to be multifactorial, although some cases may be due to teratogenic exposure, such as maternal diabetes. Therefore, VACTERL association is not considered a genetic syndrome and should be considered a diagnosis of exclusion. In individuals for whom a diagnosis of VACTERL association is entertained, chromosomal microarray and chromosomal breakage studies for Fanconi anemia should be considered. Other genetic syndromes associated with EA/TEF include CHARGE syndrome, Down syndrome, trisomy 18, and other chromosomal abnormalities (**Table 11**).[3,7–9,25,34–37]

VENTRAL WALL DEFECTS

Omphalocele and gastroschisis are the most common congenital ventral wall defects. Omphalocele is a midline defect characterized by eviscerated abdominal contents, which are covered by a protective sac. Omphalocele is associated with other anomalies in up to 90% of cases. Chromosomal abnormalities, including aneuploidies, occur in approximately 20% of cases.[38,39] Beckwith-Wiedemann syndrome, CHARGE syndrome, and VACTERL association are the most common genetic conditions associated with omphalocele (**Table 12**).[5–7,25,36] In infants with omphalocele, careful examination for other anomalies, including cardiac, renal, and ophthalmologic, should be considered. In the absence of findings that point to a specific syndrome (ie, Beckwith-Wiedemann syndrome), chromosomal microarray testing should be considered.

In contrast, the viscera in gastroschisis are not covered by a sac and protrude through a defect typically located just to the right of the umbilicus. Occasionally the sac covering an omphalocele can rupture, giving the appearance of gastroschisis, but the location of the ventral wall defect can be used to determine whether the most likely diagnosis is a ruptured omphalocele or gastroschisis. Gastroschisis is associated with young maternal age and maternal exposure to tobacco, alcohol, and ibuprofen. Gastroschisis may be associated with intrauterine growth restriction and prematurity.[40] Gastroschisis often occurs as an isolated defect but can have associated anomalies in up to one-third of cases. The most common associated anomalies are intestinal atresias, although musculoskeletal, cardiac, urogenital, and other gastrointestinal defects may be present.[39] For infants who have apparently isolated gastroschisis or gastroschisis associated only with intestinal atresia, genetic testing is typically normal and recurrence risks are low.

POLYDACTYLY

Polydactyly is a common congenital anomaly and can occur on the ulnar (postaxial) or the radial (preaxial) aspects of the extremities. Of the 2 types, postaxial polydactyly is

Table 10
Cardiac defects and associated genetic syndromes

Cardiac Defect	Genetic Syndrome	Associated Features	Potential Evaluations	Potential Genetic Studies
Atrial septal defect	Holt-Oram	Upper limb malformation Cardiac conduction disease	Upper limb radiographs Echocardiogram	Sequencing of *TBX5*
Atrioventricular canal	Down (trisomy 21)	Up-slanting palpebral fissures 5th-Finger clinodactyly Single transverse palmar creases Increased gap between 1st and 2nd toes	Audiology evaluation Complete blood cell count Ophthalmologic evaluation Thyroid function tests	Routine chromosome analysis
Coarctation of the aorta	Kabuki	Long palpebral fissures Large ears Spinal column abnormalities Postnatal growth deficiency	Ophthalmologic evaluation Renal ultrasound Spine radiographs	Sequencing of *KMT2D* and *KDM6A*
	Turner	Webbed posterior neck Broad chest with wide-spaced nipples Lymphedema of hands and feet	Audiology evaluation Renal ultrasound Thyroid function tests	Routine chromosome analysis
Hypoplastic left heart syndrome	Turner	Webbed posterior neck Broad chest with wide-spaced nipples Lymphedema of hands and feet	Audiology evaluation Renal ultrasound Thyroid function tests	Routine chromosome analysis
Interrupted aortic arch	22q11 Deletion	(See Table 5)	(See Table 5)	(See Table 5)
Peripheral pulmonary artery stenosis	Alagille	Bile duct paucity Butterfly vertebrae Posterior embryotoxon	Abdominal ultrasound Chest radiographs Liver function tests Ophthalmologic evaluation	Sequencing of *JAG1*

Pulmonary valve stenosis	Noonan	Tall forehead Hypertelorism Down-slanting palpebral fissures Low-set, posteriorly rotated ears Excess nuchal skin Low posterior hairline	Ophthalmologic evaluation Renal ultrasound	Molecular testing: at least 12 genes, including *PTPN11* (multigene panel testing available)
Supravavular aortic stenosis	Williams	Hypercalcemia Hypotonia Peripheral pulmonic stenosis Failure to thrive Renal artery stenosis	Bladder and kidney ultrasound Calcium level Ophthalmologic evaluation	Microarray or deletion testing for 7q11.23
Tetralogy of Fallot	22q11 Deletion	(See Table 5)	(See Table 5)	(See Table 5)
Ventricular septal defect	Down (trisomy 21)	(See previously)	(See previously)	(See previously)
	22q11 Deletion	(See Table 5)	(See Table 5)	(See Table 5)

Table 11
Tracheoesophageal fistula and associated conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Infant of a diabetic mother	(See Table 1)	(See Table 1)	(See Table 1)
Down (trisomy 21)	(See Table 10)	(See Table 10)	(See Table 10)
CHARGE	(See Table 9)	(See Table 9)	(See Table 9)
Chromosomal abnormalities	(See Table 1)	(See Table 1)	(See Table 1)
Fanconi anemia	Microcephaly Short stature Pigmentary abnormalities Thumb abnormalities (absent/ hypoplastic, bifid, duplicated, etc.) Other upper extremity abnormalities Lower extremity abnormalities Genitourinary abnormalities Pancytopenia	Hematologic studies including complete blood count and bone marrow aspirate Renal ultrasound	Chromosomal breakage studies Molecular testing; at least 16 genes, including *FANCA* and *BRCA2*
Trisomy 18	(See Table 2)	(See Table 2)	(See Table 2)
VACTERL association	Vertebral defects Anal atresia/imperforate anus Cardiac defects TEF Limb anomalies Renal anomalies	Abdominal radiographss AP and lateral radiographs of the entire spine Echocardiogram Radiographs of affected limbs Renal ultrasound	None

Abbreviation: AP, anterior-posterior.

Table 12
Ventral wall defects and associated conditions

Type of Defect	Genetic Syndrome	Associated Features	Potential Evaluations	Potential Genetic Studies
Omphalocele	Beckwith-Wiedemann	(See Table 1)	(See Table 1)	(See Table 1)
	CHARGE	(See Table 9)	(See Table 9)	(See Table 9)
	Trisomy 13	(See Table 2)	(See Table 2)	(See Table 2)
	Trisomy 18	(See Table 2)	(See Table 2)	(See Table 2)
	VACTERL	(See Table 11)	(See Table 11)	(See Table 11)
Gastroschisis	None	Cardiac anomalies Intestinal atresia Genitourinary anomalies Musculoskeletal anomalies	Abdominal radiographs Echocardiogram Renal ultrasound Skeletal radiographs	None

the most common. Postaxial polydactyly can manifest as a fully developed digit (type A) or as a rudimentary cutaneous appendage (type B). Type B polydactyly generally occurs as an isolated autosomal dominant condition with reduced penetrance. It is more common in African American individuals, with a prevalence of 1 in 143 live births versus 1 in 1339 in white infants. Type B polydactyly frequently occurs bilaterally. It is commonly treated in the nursery with suture ligation.[41–43]

In contrast, preaxial polydactyly is less common, with a prevalence of up to 1 in 3000 live births but occurs more frequently in white infants. It also is associated with an increased incidence of systemic conditions, such as Fanconi anemia, chromosomal abnormalities, and VACTERL association (**Table 13**).[36,37] Therefore, the finding of preaxial polydactyly should prompt a thorough evaluation for other congenital anomalies and consideration of genetic testing for Fanconi anemia (chromosomal breakage studies) at a minimum.[41,42]

Table 13
Preaxial polydactyly and associated conditions

Differential Diagnosis	Associated Features	Potential Evaluations	Potential Genetic Studies
Fanconi anemia	Microcephaly Short stature Pigmentary abnormalities Thumb abnormalities (absent/hypoplastic, bifid, duplicated, etc.) Other upper extremity abnormalities Lower extremity abnormalities Genitourinary abnormalities Pancytopenia	Hematologic studies including complete blood count and bone marrow aspirate Renal ultrasound	Chromosomal breakage studies Molecular testing; at least 16 genes, including *FANCA* and *BRCA2*
VACTERL association	(See Table 11)	(See Table 11)	(See Table 11)

SUMMARY

Neonatologists often have the unique opportunity to be the first to identify abnormalities in the neonate. Once a particular anomaly has been identified in a patient, a thorough examination with particular attention to other associated anomalies should be pursued, taking into consideration a patient's age, gender, race, and family history. **Tables 1–13** summarize the anomalies discussed in this review, possible associated syndromes and findings, and suggested investigations. The ability to recognize anomalies and their associated conditions can be the key to the diagnosis and management of a patient and to appropriate recurrence risk counseling for the family.

Best Practices

What is the current practice?

Chromosomal microarray is the recommended first-line test for infants with dysmorphic features that are not specific to a well-recognized genetic syndrome.[44] A genetics consultation should also be considered.

What changes in current practice are likely to improve outcomes?

Making a diagnosis in a child with dysmorphic features enables providers to recognize occult malformations and provide surveillance for complications that may develop over time. It also provides families information regarding the prognosis for their child and recurrence risks for future pregnancies.[2]

Major Recommendations

Whenever a dysmorphic feature is recognized, a comprehensive examination for the presence of other anomalies must be undertaken. If there are other features of a well-delineated syndrome present, further evaluation, including a detailed family history, diagnostic studies, and genetic testing, should be pursued (refer to **Tables 1–13** for examples and further information).

If features of a well-delineated syndrome are not recognized but there are at least 3 minor anomalies present, further evaluation, including a detailed family history and a chromosomal microarray, should be obtained. Also, the patient should be evaluated for the presence of an occult major malformation, because the presence of 3 or more minor anomalies is associated with a significantly increased risk of the occurrence of an occult major malformation.[2]

Rating for the Strength of the Evidence

Chromosomal microarray is the first-line test for infants with dysmorphic features that are not specific to a well-recognized genetic syndrome per the ACMG guidelines.[44] This test has a diagnostic yield of 15% to 20%.[8]

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Summary statement

Whenever a dysmorphic feature is recognized, a comprehensive evaluation for the presence of other dysmorphic features and a possible underlying genetic syndrome must be undertaken to help guide management and provide appropriate counseling to the family.

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