Dysmorphology

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Education Gaps

1. Children and families affected by genetic conditions frequently experience protracted diagnostic odysseys requiring the use of complex esoteric tests.
2. A recent survey of the American Academy of Pediatrics membership revealed that pediatricians are aware of the importance of genetic medicine. However, it also revealed that medical training has not prepared most of them to direct genetic evaluations and order genetic testing.
3. Referrals to genetic subspecialists for evaluation, counseling, and testing can be challenging for patients and their families.
4. The rapid evolution of genetic medicine, including the number of known genetic conditions and the availability of diagnostic testing methods, necessitates ongoing education.

Objectives After completing this article, readers should be able to:

1. Recognize a distinctive pattern of dysmorphic features concerning for a genetic condition.
2. Construct a genetic differential diagnosis through the use of resources such as the Online Mendelian Inheritance in Man® database and literature review.
3. Appreciate the complexities of genetic testing and discussing the results.
4. Demonstrate familiarity with the clinical findings of CHARGE syndrome, Cowden syndrome, and Loeys-Dietz syndrome.
5. Appreciate the importance of newborn screening and the availability of resources such as ACTion sheets and confirmatory algorithms for pediatricians.

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ABBREVIATIONS

CHARGE	coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, ear anomaly
OMIM	Online Mendelian Inheritance in Man
POSSUM	Pictures of Standard Syndromes and Undiagnosed Malformations

INTRODUCTION

It is time to stop thinking of genetic medicine as only applicable to a small set of rare diseases affecting a limited cohort of patients. Although individual genetic diagnoses are rare, their aggregate effect on human health is not. An estimated 8% of

live births are affected by a Mendelian condition, which is associated with variation in a single gene, and/or a congenital anomaly. (1) In addition, the molecular basis is now known for more than 6,500 Mendelian conditions, genetic susceptibilities, and other phenotypes. (2) As this number continues to increase, so will the challenges facing clinicians tasked with integrating genetic medicine into the individualized care of their patients. It is impossible to know the epidemiology, pathogenesis, clinical aspects, management, and prognosis for all known genetic conditions. And even when a clinician knows everything there is to know about a specific genetic condition, this knowledge may be inadequate if the evidence base is limited by the genetic condition's relative rarity and/or recent discovery.

As a group, pediatricians have long recognized the importance of genetic medicine, including use of the family history to inform patient care. We also recognize the limitations of our training and time for incorporating genetic evaluation and management principles into routine clinical practice. For example, a recent survey of the American Academy of Pediatrics membership revealed that 53.1% of respondents identified inadequate training and/or practice guidelines for genetic test selection, 60.2% regarding genetic test interpretation, and 57.4% regarding ongoing genetic management. Furthermore, 48.9% identified inadequate time for genetic test interpretation. These concerns cannot be addressed with referrals alone. (3) The referral process is often complicated by long wait times and travel distances, which are likely exacerbated by the continued scarcity of genetic subspecialists. (4)(5)

Despite these difficulties, incorporating genetic medicine into the standard of care has the potential to revolutionize and individualize patient care. Overcoming current barriers will likely necessitate ongoing education and innovative approaches that cross medical subspecialty and geographic boundaries. For example, the American College of Medical Genetics and Genomics ACTion Sheets and Confirmatory Algorithms (http://www.ncbi.nlm.nih.gov/books/NBK55827/) are available to pediatricians who have received abnormal newborn screen results concerning for an inborn error of metabolism, free of charge. (6) Additional resources that may be available in the future include telemedicine programs and other technology-enabled systems.

But for now, what should a pediatrician do when encountering a distinctive-appearing child with dysmorphic features?

PATIENT 1

You are performing the admission history and physical examination for a previously healthy 7-year-old boy with a working diagnosis of community-acquired pneumonia. His respiratory rate is 55 breaths/min on nasal cannula. The remainder of his physical examination seems normal at first. You then notice penile freckling.

PATIENT 2

You are evaluating a 2-week-old girl, born at term, for her first well-baby check. She has been feeding, voiding, and stooling well. Her physical examination is mostly reassuring. She is pink and vigorous. You then notice widely spaced eyes, increased joint laxity, and a bifid uvula (Fig 1).

DYSMORPHOLOGY

Dysmorphology was first described by David W. Smith in 1966 as the "study of, or general subject of, abnormal development of tissue form." His intention for defining it in this manner was to encourage an approach that did not presume an environmental cause, as is the case with teratology. (7) Since then, dysmorphology has evolved into a discipline that addresses the variation of physical features with increasing precision. The Elements of Morphology (https://elementsofmorphology.nih.gov) is a resource that delineates the standardized nomenclature for the description of physical features, and it is available free of charge. (8) The importance of clearly defined and consistent terminology is easily demonstrated. Describing an ear as abnormal is neither significant nor specific. A detailed description can be both. For example, a short and wide ear with a cuplike overall configuration, triangular concha, and discontinuous antihelix and antitragus is suggestive of CHARGE syndrome. The acronym

Figure 1. Example of a bifid uvula.

CHARGE represents the clinical findings that are classically described with this genetic condition: coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, and ear anomaly (Fig 2). If there is specific concern for CHARGE syndrome, then *CHD7* gene testing can be performed to confirm the diagnosis. (9)(10) In this illustrative scenario, genetic dysmorphology has been used to describe an observable physical feature, recognize this feature as suggestive of a specific diagnosis, and answer the question "Is this genetic?" In practice, a genetic evaluation requires systematic consideration of the family history, clinical findings, identifiable patterns, differential diagnoses, and optimal genetic testing strategy.

Understanding a patient's family history is fundamental to dysmorphology because the family history informs the baseline likelihoods of specific genetic diagnoses for specific clinical findings. Taking a family history is useful, regardless of whether it is considered positive or negative. A family history can be considered positive if it fulfills the Rule of Two/Too described by Robert A. Saul. This includes 2 or more affected family members, 2 or more affected generations, too many clinical findings, and too early age at onset. (11) When the family history is visually represented in the form of a pedigree, there may be a recognizable inheritance pattern (Table 1). A positive family history is suggestive of an inherited genetic trait and can facilitate a focused genetic evaluation. For example, a young girl with mucocutaneous melanocytic macules can be diagnosed as having Peutz-Jeghers syndrome if her father is known to be affected. (12) In contrast, an ostensibly negative family history does not exclude the possibility of an inherited genetic trait. For example, a common theme of the earlier studies describing Alagille syndrome was the subsequent diagnosis of seemingly unaffected parents. (13) Furthermore, a negative family history may actually be positive if the inheritance pattern is not as obvious as the autosomal dominant pattern. These include autosomal recessive, both the typical male-predominant and the atypical female-predominant X-linked, and matrilineal mitochondrial patterns. (14)(15) Ultimately, even the absence of a positive family history is informative because it suggests against the possibility of a genetic diagnosis that is expected to be familial in a significant percentage of cases.

As demonstrated by the example of the "abnormal" ear suggestive of CHARGE syndrome, differences in observable physical features can be suggestive of specific genetic etiologies. However, not all anomalies are specific and/or significant, and there are a few different types to consider (Table 2). A malformation is a "morphologic defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process". (16) A disruption is a "morphological defect of an organ, part of an organ, or a larger region of the body

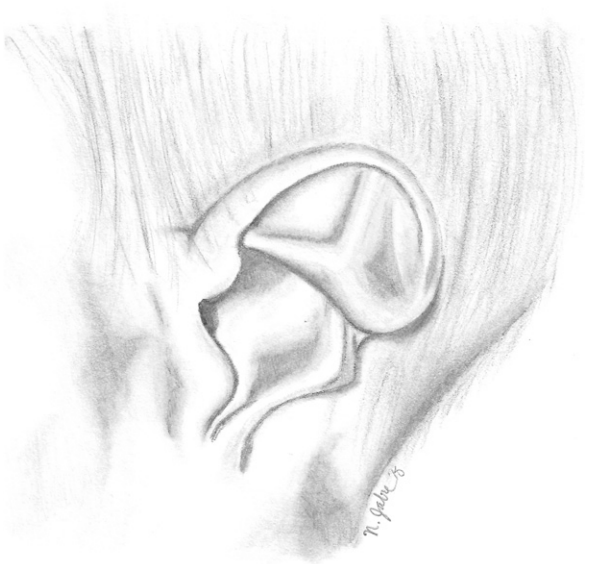


Figure 2. Example of a CHARGE ear.

TABLE 1. **Examples of Recognizable Inheritance Patterns**

Autosomal dominant
Typically has multiple affected individuals in a single generation
Typically has similar manifestations and severity in females and males
Typically has multiple generations involved, without "skipping" of generations
Autosomal recessive
Typically has multiple affected individuals in a single generation
Typically has similar manifestations and severity in females and males
When multiple generations are involved, typically has "skipping" of generations
X-linked
Typically has multiple affected individuals in a single generation
Typically has more manifestations with higher severity in males than in females
When multiple generations are involved, never has father-to-son transmission
Mitochondrial
Typically has multiple affected individuals in a single generation
Manifestations and/or severity are not typically dependent on biological sex, can be variable
When multiple generations are involved, always has mother-to-child transmission

resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process". (16) A deformation is an "abnormal form, shape, or position of a part of the body caused by mechanical forces". (16) A dysplasia is an "abnormal organization of cells into tissue(s) and its morphologic result(s)". (16) If an observed anomaly can be conceptualized as a malformation or a dysplasia, then a genetic etiology can be considered more likely. In contrast, if an anomaly can be conceptualized as a disruption or a deformation, then an environmental etiology can be considered more likely. Anomalies can also vary in significance. Those that are expected to affect a patient's health can be considered major anomalies. Those that are not expected to affect a patient's health can be considered minor anomalies.

Observable physical features can vary in number, size, placement, and shape. For example, an ear can be missing, measure less than the third percentile for age, be borderline low-set, have a squared superior portion of the helix, etc. It can be helpful to quantify objective differences, which are typically more important than subjective ones. The *Handbook of Physical Measurements* and *Smith's Recognizable Patterns of Human Malformation* are references that can be used to learn how to measure a body part and then compare this measurement with published standards. (17)(18) Any differences in a child's overall growth and development are important clues to consider as well. It can be challenging to determine the significance of anomalies beyond any major or minor medical implications. For example, polydactyly is a common anomaly that can be observed in isolation and in the context of more than 300 genetic syndromes. (19) The significance of this finding is determined by its specific characteristics and by the contexts of family- and population-level variability. Type B postaxial polydactyly, which consists of a rudimentary sixth digit arising from the ulnar/fibular aspect of the fifth digit, has been observed at a frequency approaching 1 in 100 in specific ethnic populations and 1 in 3,000 in others. (20) Predictably, this form of polydactyly is typically expected to be an isolated finding but to differing degrees depending on ethnicity.

It is also important to consider anomalies in the context of others and to identify patterns suggestive of specific genetic and environmental causes, including developmental field defects, sequences, syndromes, and associations (Table 3). A developmental field defect is a "pattern of anomalies derived from the disturbance of a single developmental field". (16) A sequence is a "pattern of multiple anomalies derived from a single known or presumed previous anomaly or mechanical factor". (16) A syndrome is a "pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence" or developmental field defect. (16) An association is a "nonrandom occurrence in 2 or more individuals of multiple anomalies not known to be" a developmental field defect, a sequence, or a syndrome. (16) In some cases, a pattern may be suggestive of a specific genetic diagnosis in the same way that abdominal pain, joint pain, and purpuric lower extremity exanthema are suggestive of Henoch-Schonlein purpura. (21) For a limited set of genetic conditions, the characteristic clinical findings have informed the development of online tools, including the Marfan syndrome systemic score calculator and the *PTEN*-specific risk calculator. The former determines whether a patient meets the diagnostic criteria for Marfan syndrome. Marfan syndrome is characterized by connective tissue changes, including aortic dilation, myopia, and scoliosis. The latter estimates the likelihood that *PTEN* gene testing for Cowden syndrome will be positive. Cowden syndrome is characterized by macrocephaly, a variety of mucocutaneous findings, and cancer predisposition. Access to both is available free of charge. (22)(23) It is possible that additional online tools will be developed over time and with funding.

If the pattern of clinical findings is not immediately evocative of a specific diagnosis, then it is critical to adopt an open-minded approach to the genetic differential diagnosis. This is exemplified by the set of questions ascribed to pediatrician and geneticist Barton Childs: "Why this patient? Why this disease?

TABLE 2. **Examples of Anomaly Types**

Malformation
Morphologic defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process.
Example: atrioventricular septal defect (ie, failure of the endocardial cushions to form the atrial and ventricular septa)
Disruption
Morphologic defect of an organ, part of an organ, or a larger region of the body resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process.
Example: amniotic bands (ie, minor to major disfigurement and/or amputation affecting a single body part or multiple body parts)
Deformation
Abnormal form, shape, or position of a part of the body caused by mechanical forces.
Example: Potter facies (ie, combination of flattened facial profile and nose, epicanthal and infraorbital folds, low-set ears, and recessed chin)
Dysplasia
Abnormal organization of cells into tissue(s) and its morphologic result(s).
Example: thanatophoric dysplasia (ie, severe genetic condition affecting the development of the axial and appendicular skeleton, often but not always lethal)

Why now?" These questions may seem open-ended to a fault. However, this "genetic lens" is crucial for considering the genetic and environmental factors influencing a patient's clinical presentation, including timing. (24) There is a growing collection of paper-based and electronic resources available to facilitate this process. For example, the Online Mendelian Inheritance in Man® (OMIM®; Johns Hopkins University, Baltimore, MD) database is a powerful and up-to-date tool that can highlight genetic conditions to consider based on 1 or more clinical findings. Access to this resource is available free of charge. (2) The POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) and London Dysmorphology databases can be used to generate a list of diagnoses associated with specific dysmorphisms as well. (25)(26) Access to the latter resource is available free of charge through the Face2Gene smartphone application. Face2Gene uses automated facial feature analysis, in addition to the manual entry of clinical findings, to facilitate the construction of a genetic differential diagnosis. (27) When there is a history of in utero exposure(s), resources such as the Reprotox® and TOXNET® databases can be referenced. (28)(29) Access to the latter resource is available free of charge.

It can be worthwhile to systematically think through the different types of genetic variation that are possible when constructing the genetic differential diagnosis. This thought exercise is useful for ensuring that a variety of diagnoses are considered and for determining the type(s) of genetic testing that may be indicated for a patient's genetic evaluation (Table 4). A whole chromosomal aneuploidy is an extra or missing chromosome. This becomes more likely with a history of advanced maternal age. A chromosomal rearrangement is a change in the location of a piece of a chromosome. This becomes more likely with a history of recurrent pregnancy losses. A partial chromosomal structural variant is an extra or missing piece of a chromosome. This should be considered with a history of developmental delay, autism spectrum disorder, and/or multiple congenital anomalies. A single-gene variant is a change in a gene within the nuclear genome. This becomes more likely with a history of advanced paternal age, a positive family history, a specific pattern of clinical findings, etc. An imprinting variant is an extra or missing parent-of-origin–specific methylation. This becomes more likely with a history of assisted reproductive technologies. A mitochondrial genomic variant is a change in a gene within the mitochondrial genome. This becomes more likely with a positive family history suggestive of matrilineal mitochondrial inheritance.

For example, there are many genetic conditions associated with "abnormal ears" and other anomalies. Down syndrome can be characterized by small dysplastic ears, redundant nuchal skin, a protruding tongue, a flattened facial profile, epicanthal folds, an increased sandal gap, and hypotonia. It is associated with trisomy 21 or chromosomal rearrangements. (30) 22q11.2 deletion syndrome can be characterized by dysplastic ears, congenital heart defect, cleft palate, learning difficulties, immunodeficiency, seizures, and hypocalcemia. It is associated with partial deletion of chromosome 22. (31) CHARGE syndrome can be characterized by dysplastic ears and a variety of other anomalies, as previously discussed. It is associated with changes in the *CHD7* gene (and possibly also the *SEMA3E* gene). (32)(33) Beckwith-Wiedemann syndrome can be characterized by posterior helical pits, overgrowth, omphalocele, and risk of embryonal tumors. It is associated with a variety of changes involving imprinted

TABLE 3. **Examples of Anomaly Patterns**

Developmental field defect
Pattern of anomalies derived from the disturbance of a single developmental field.
Example: caudal regression (ie, atypical development of the lower half of the body, including the extremities)
Sequence
Pattern of multiple anomalies derived from a single known or presumed previous anomaly or mechanical factor.
Example: Pierre-Robin sequence (ie, micrognathia, leading to glossoptosis, leading to airway obstruction, often leading to cleft palate)
Syndrome
Pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence or developmental field defect.
Example: CHARGE syndrome (ie, coloboma, heart defect, choanal atresia, restricted growth, genitourinary anomaly, ear anomaly)
Association
Nonrandom occurrence in ≥2 individuals of multiple anomalies not known to be a developmental field defect, a sequence, or a syndrome.
Example: VACTERL association (ie, vertebral anomaly, anal atresia, cardiac anomaly, tracheoesophageal fistula, renal anomaly, limb anomaly)

domains on chromosome 11. (34)(35) Mitochondrial genomic variants are less likely when considering the genetic differential diagnoses for ear anomalies but more likely when considering that for nonsyndromic sensorineural hearing loss. (36)(37) Mycophenolate mofetil embryofetopathy can be associated with anotia or other ear anomalies, ocular anomalies, and orofacial clefting; it is a consequence of teratogenic exposure. (38)

Once the genetic differential diagnosis has been constructed and carefully considered, then the optimal genetic testing strategy can be planned. This often includes a chromosomal microarray, which is recommended as first-line genetic testing for the genetic evaluation of multiple congenital anomalies, autism spectrum disorder, and intellectual disability. (39) It is indicated for the evaluation of possible partial chromosomal structural variant. Beyond this, the approach to genetic testing should be focused on the most likely genetic conditions and/or types of genetic variation. Karyotype is indicated for the evaluation of possible whole chromosomal aneuploidy or chromosomal rearrangement. Single- or multi-gene testing is indicated for the evaluation of possible single-gene variant. Methylation analysis is indicated for the evaluation of possible imprinting variant. Mitochondrial gene testing is indicated for the evaluation of possible mitochondrial genomic variant. It is important to ask about and learn of previous genetic testing before ordering a genetic test. Repeating a genetic test is not expected to yield a different result, only added cost and several weeks' delay to the patient's genetic evaluation. As a result, the 5 recommendations by the American College of Medical Genetics and Genomics through the Choosing Wisely® campaign include "Do not order a duplicate genetic test for an inherited condition unless there is uncertainty about the validity of the existing test result." (40) It is worth having any previous genetic testing results available. Word-of-mouth reports can be unreliable, and unhelpful during discussions with consultants. A few of the additional intricacies of genetic testing are addressed in the article "Genetic Counseling in Pediatrics" published in the July 2018 issue of *Pediatrics in Review*. (41)

Precise word choice is critical when communicating with patients and their families regarding genetic test results and diagnoses. For example, a "positive" test result may not be considered good news by parents dreading the possibility that their child has a genetic "disorder." In contrast, a "negative" test result may be considered bad news by parents pursuing an end to their child's "diagnostic odyssey." Value-laden terms such as *disorder* can be avoided by adopting the words the family uses or more neutral options such as *condition*. Furthermore, it is important to remember that patients are not defined by their genetic conditions. Many may not even consider themselves to have a condition. For example, the National Association

TABLE 4. **Examples of Genetic Variation Types**

Whole chromosomal aneuploidy
An extra or missing chromosome
Genetic testing: karyotype analysis
Chromosomal rearrangement
A change in the location of a piece of a chromosome
Genetic testing: karyotype analysis
Partial chromosomal structural variant
An extra or missing piece of a chromosome
Genetic testing: chromosomal microarray analysis
Single-gene variant
A change in a gene within the nuclear genome (eg, nucleotide sequence change, extra piece, missing piece), repeat expansion
Genetic testing: single-gene sequencing and/or deletion/duplication analysis, multi-gene panel sequencing and/or deletion/duplication analysis, clinical exome sequencing, repeat expansion analysis
Imprinting variant
Extra or missing methyl group modification
Genetic testing: DNA methylation analysis
Mitochondrial genomic variant
A change in a gene within the mitochondrial genome (eg, nucleotide sequence change, missing piece)
Genetic testing: mitochondrial genome sequencing and/or deletion analysis

of the Deaf prefers to define the term *deaf* as the "audiological condition of not hearing" and the term *Deaf* as the "particular group of deaf people who share a language—American Sign Language (ASL)—and a culture." (42) Similarly, the Little People of America has advocated for the use of their given names or preferred terms such as *little people* and *dwarfs*. (43) Communication of genetic information benefits from a thoughtful approach such as the SPIKES protocol for disclosing information in the oncology setting. The acronym SPIKES represents the 6 steps of the protocol: 1) Setting up the interview, 2) Assessing the patient's perception, 3) Obtaining the patient's invitation, 4) Giving knowledge and information, 5) Addressing the patient's emotions with empathetic responses, and 6) Strategy and summary. (44)

PATIENT 1 REVISITED

The family history is notable for multiple paternal relatives with macrocephaly. You acknowledge that larger heads can run in families and not amount to anything beyond difficulties finding hats that fit. However, you identify additional concerns. His paternal aunt was diagnosed as having breast cancer at 37 years old. His paternal grandfather was diagnosed as having nonmedullary thyroid cancer recently. This seems like too many things affecting more than 2 relatives. There is a clear autosomal dominant inheritance pattern. Additional careful questioning reveals that his father also has penile freckling. You measure the child's head circumference, which is beyond the 95th percentile for age and sex. A quick query of OMIM for these features suggests the diagnosis of Cowden syndrome. You also find the online *PTEN*-specific risk calculator, which suggests a high probability of finding a pathogenic variant. (23) You refer your patient and his family for genetic counseling and *PTEN* gene testing. After a few weeks, the diagnosis of Cowden syndrome is molecularly confirmed for him, his father, and several paternal relatives. At first, the entire family finds it hard to handle this life-changing information. However, it also means that his 35-year-old father undergoes screening colonoscopy in time to have a precancerous lesion removed. (45)

PATIENT 2 REVISITED

The family history seems unremarkable. However, you remind yourself that traits can be genetic but not inherited. Her hypertelorism, hypermobility, and bifid uvula seem specific, and potentially significant. For example, although isolated bifid uvula can be observed in the general population, your literature review reminds you that it may be a marker of submucous cleft palate. A submucous cleft palate can be difficult to detect and has surgical implications. (46)(47) A quick query of OMIM for these features suggests several possible diagnoses, including spondylodysplastic Ehlers-Danlos syndrome, Shprintzen-Goldberg syndrome, and 3 different types of Loeys-Dietz syndrome. As you review the OMIM clinical synopsis for each genetic condition, it seems difficult to determine which is the most likely because many of the clinical findings are nonspecific. However, you identify several "can't miss" cardiovascular anomalies. You refer your patient for genetic evaluation and order an echocardiogram, which reveals a bicuspid aortic valve. By the time she is seen by the geneticist and genetic counselor she has more noticeable arachnodactyly and velvety skin. The family elects to proceed with *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* gene panel testing for Loeys-Dietz syndrome. After a few weeks, her parents are notified that she has a de novo pathogenic variant in the *TGFBR2* gene. A repeated echocardiogram reveals aortic root dilation. She begins treatment with an angiotensin receptor blocker under the guidance of an expert in genetic aortopathies. She tolerates this well as her aortic root diameter *Z* score stabilizes, then normalizes. (48)

CONCLUSION

A genetic diagnosis can have life-changing implications for our patients and their families. However, the diagnostic odyssey undertaken to reach this point is often protracted. It can take a few years for patients to receive a diagnosis, even for those with well-described genetic conditions such as 22q11.2 deletion syndrome. (49) This process may involve multiple subspecialists and misdiagnoses when the clinical picture is complex and/or characterized by nonspecific findings, as is often the case with primary mitochondrial conditions. (50) It is important to remember that the natural variation in physical features, further influenced by familial resemblances and ethnicity, can obscure the classical craniofacial features described for genetic conditions such as 22q11.2 deletion syndrome. (49) As is the case with other pediatric presentations, syndromic patterns of distinctive findings require systematic responses. Even when the possibility of a genetic condition is recognized and a referral is placed, patients and their families often need to wait for several months for an appointment with a geneticist. This process is sometimes driven by mothers and fathers seeking answers, often without medical expertise, but always with expertise in their children. With time, they often develop a familiarity with rare and ultra-rare conditions that can surpass that of most health-care professionals and scientists. (51) In these cases, the pediatrician can partner with these families, listen to their concerns, and work toward timely evaluation. This may include basic laboratory and imaging studies.

Several approaches are poised to address the need for genetics services. For example, telemedicine has been used to improve access and has been well-received. (52) There is increasing patient interest in the use of social media, at least for the

purposes of increasing awareness and education. (53) It is possible that general pediatrician-driven genetic evaluations will be facilitated and/or necessitated by continued development of the newborn screening program and its associated resources. (6) For example, a recent multistate study explored the possibility of newborn screening for fragile X syndrome. (54) Eventually, general pediatrician involvement in other standardized genetic evaluations and treatment may become common practice.

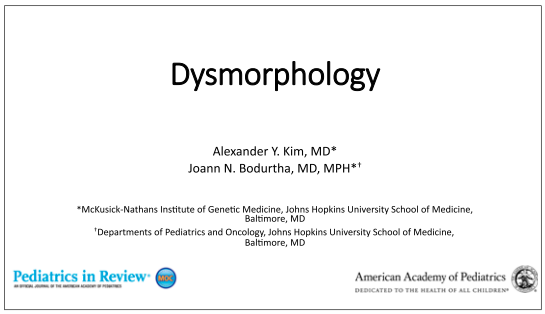
Currently available online resources such as the OMIM database have revolutionized the genetic diagnostic process. (2) Automation and standardization of other difficult and time-consuming processes are likely to play a role in the future, including facial feature analysis with smartphone applications and basic genetic counseling with chatbots. (27)(55) It is possible to use natural language processing for the automated extraction of family history data from the electronic medical record. (56) It is also possible to automate the identification of high-risk pedigrees collected using online family history tools, as well as subsequent referrals. (57) Eventually, it may be possible to interrogate the electronic medical record data and use Bayesian frameworks to automatically generate probability-ranked differential diagnoses. (58) Quantitative mathematical approaches such as this are potentially applicable to the analysis of expansive genomic data for variant pathogenicity assessments as well. (59) It is even possible that all newborns will be screened for genetic conditions using exome sequencing or another paradigm-shifting test method not yet dreamed up. (60)

As genetic medicine continues to rapidly evolve, we must remember, as articulated by Judith G. Hall: "Each family seen in the clinic has been through emotional trauma, is facing difficult decisions, and will end up with less than ideal solutions. Remaining sensitive and open is challenging and requires training and practice. Providing the relevant information clearly and ensuring that each family member feels supported are special skills. Dealing with such significant problems might seem depressing, but providing families with new perspectives, multiple options, and reliable information for their life journey is enormously rewarding." (51)

Summary

- Based on level D evidence (expert opinion, case reports, reasoning from first principles), dysmorphology is an art and science of precise clinical reasoning that addresses the variation of physical features. (7)(16)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), the family history is an important source of genetic information. Recognizable inheritance patterns include autosomal dominant, autosomal recessive, X-linked, and mitochondrial genomic. (11)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is useful to consider the different types of genetic and nongenetic changes that are associated with physical changes when constructing genetic differential diagnoses, which ultimately determines the optimal genetic testing strategy.
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), resources available to pediatricians include the Elements of Morphology, the *Handbook of Physical Measurements, Smith's Recognizable Patterns of Human Malformation,* the Online Mendelian Inheritance in Man® database, and the London Dysmorphology database (available through the Face2Gene smartphone application). (2)(8)(17)(18) (27)
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is important to ask about and learn of any previous genetic testing before ordering a genetic test.
- Based on level D evidence (expert opinion, case reports, reasoning from first principles), it is important to be precise and careful in word choice when discussing genetic testing results and genetic diagnoses.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/40/12/609.supplemental.**



SUGGESTED QUALITY IMPROVEMENT PROJECT

- Standardized inclusion of family history information in the assessments of infants, children, and adolescents.

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References for this article are at http://pedsinreview.aappublications.org/content/40/12/609.

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1. You are seeing a 7-year-old girl in your office who is new to your practice. She comes with her mother and father. The child has multiple café-au-lait macules and axillary and inguinal freckles. She has normal growth parameters. She is receiving an Individualized Education Plan for reading. Her parents do not have any café-au-lait macules or axillary/inguinal freckles. Which of the following is the most accurate statement regarding the potential diagnosis given this child's clinical findings?
    A. Genetic testing for neurofibromatosis type 1 (NF1) will provide a definitive answer as to whether this child has NF1.
    B. Given the absence of neurofibromas at this age, a diagnosis of NF1 is unlikely.
    C. NF1 is unlikely because this is an autosomal dominant condition and she would have had to inherit her *NF1* gene from her mother or father.
    D. The absence of a negative family history of NF1 does not rule out the possibility of a diagnosis of NF1.
    E. The risk of this child's future offspring having NF1 is negligible given the uncertainty of a clinical diagnosis.
2. You are called to the delivery room to attend the delivery of a baby boy born to a 25-year-old gravida 1 para 0 woman. Her pregnancy was complicated by oligohydramnios and renal agenesis. The baby is born vaginally with Apgar scores of 7, 5, and 3 at 1, 5, and 10 minutes, respectively. The baby is intubated and transferred to the NICU. On physical examination he was noted to have midface flattening, multiple joint contractures, and hip dysplasia. Which of the following statements best describes the pathophysiologic cause(s) of the clinical features in this patient?
    A. Amnion disruption.
    B. Early urethral obstruction sequence.
    C. Multiple deformations only.
    D. Single malformation only.
    E. Single malformation with various physical features due to deformations, secondary to the underlying malformation.
3. You are the attending covering the well-baby nursery. An African American baby boy is admitted to the nursery. He is born with postaxial polydactyly of the hands and feet. The baby's mother had no prenatal care. She denies the use of alcohol and other illicit substances or medications during pregnancy. Both parents are available. Which of the following is the most appropriate next step in this patient?
    A. Chromosome microarray study.
    B. Clinical genetics consult.
    C. Complete physical examination and family history for similar problems.
    D. Genetic testing for the *GLI3* gene.
    E. Skeletal survey.
4. A newborn female infant is transferred to the NICU shortly after birth due to polyhydramnios. On physical examination she is noted to have small dysplastic ears, redundant nuchal skin, a protruding tongue, a flattened facial profile, epicanthal folds, an increased sandal gap, and hypotonia. Family history is significant for recurrent miscarriages in the mother. Which of the following is the most appropriate genetic test to order that will most likely confirm the diagnosis in this patient?
    A. Aortopathy gene panel.
    B. DNA methylation for Prader-Willi/Angelman syndrome.
    C. Fluorescence in situ hybridization (FISH).
    D. Karyotype analysis.
    E. Subtelomeric FISH analysis.

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5. You live in a remote town and are following up with a family in which the mother has Waardenburg syndrome (a genetic condition associated with heterochromia of the eyes, hearing loss, and abnormal spacing of eyes). The mother's male child is tested for the familial genetic mutation in Waardenburg syndrome because he failed the newborn hearing screen. Genetic testing indicates that the child has a *PAX3* mutation. The geneticist calls you with the results and asks you to relay the information to the baby's family. You plan to contact the family and meet with them in person at their next clinic visit. Which of the following statements is the most appropriate way to communicate the test results to the family during your initial meeting with them?
    A. "Because your child was identified after birth with hearing loss, we suspect that he will have a more severe clinical course than his mother."
    B. "The genetic test performed indicated that your baby has the same genetic change as his mother and he is likely to have clinical features associated with Waardenburg syndrome."
    C. "The genetic test results were positive and indicate your baby has the same disease as his mother."
    D. "The genetic test results were positive for Waardenburg syndrome."
    E. "Your baby's test results for Waardenburg syndrome were positive. Your diagnostic journey is now complete."

Dysmorphology

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