RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Elements of Morphology: General Terms for Congenital Anomalies

Raoul C. Hennekam,[1]* Leslie G. Biesecker,[2] Judith E. Allanson,[3] Judith G. Hall,[4] John M. Opitz,[5] I Karen Temple,[6] John C. Carey,[5] and Elements of Morphology Consortium

[1]Departments of Pediatrics and Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

[2]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland

[3]Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Canada

[4]Departments of Medical Genetics and Pediatrics, University of British Columbia and BC Children's Hospital, Vancouver, British Columbia, Canada

[5]Division of Medical Genetics, Human Genetics, Pathology, Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah

[6]Faculty of Medicine, University of Southampton and Wessex Clinical Genetics Service, University Hospital Southampton, Southampton, United Kingdom

Manuscript Received: 20 August 2013; Manuscript Accepted: 26 August 2013

An international group of clinicians working in the field of dysmorphology has established a process for the standardization of terms used to describe human morphology. The goals are to standardize these terms and develop consensus regarding their definitions. This project will increase the usefulness and precision of descriptions of the human phenotype and facilitate reliable comparisons of phenotypic findings among clinicians and researchers in medicine, developmental biology, and genetics. Here we define and illustrate the general terms that describe congenital anomalies as related to human conditions.

Key words: nomenclature; definitions; genotype; phenotype; anomaly; variant; malformation; deformation; dysplasia; disruption; syndrome; sequence; association; morphology; dysmorphology

How to Cite this Article:
Hennekam RC, Biesecker LG, Allanson JE, Hall JG, Opitz JM, Temple IK, Carey JC, Elements of Morphology Consortium. 2013. Elements of morphology: General terms for congenital anomalies.
Am J Med Genet Part A 161A:2726–2733.

INTRODUCTION

This is the eighth in a series of papers defining the morphologic variants of the human body [Hennekam et al., 2009; Biesecker et al., 2009; Carey et al., 2009; Hall et al., 2009; Hunter et al., 2009; Allanson et al., 2009b; Hennekam et al., 2013]. Additional papers on the morphology of the limbs and trunk are in preparation. The original series was accompanied by an introductory paper describing general aspects of the project "Elements of Morphology" [Allanson et al., 2009a]. The reader is encouraged to consult the introduction when using the definitions.

The present report describes the definitions of the general terms most commonly used to describe congenital anomalies in clinical practice and research. The history of prior efforts to define the terms considered here is reviewed separately [Opitz, 2013]. In the interval since those publications, and the intervening developments of positional cloning and, now, massively-parallel sequencing, and concomitant advances in developmental biology, it became clear that an update was necessary [Carey, 2011]. We recognize that the terms (especially the terms anomaly and syndrome) are used in different ways within, and outside of, general medicine, but we limit our definitions to the description of human morphology. We have added the adjective "morphologic" to the terms anomaly and variant to indicate this, although in daily practice in dysmorphology these terms may be used without this.

Conflict of interest: none.

*Please see at the end of the manuscript for the members of the Consortium.

Grant sponsor: Intramural Research Program of the National Human Genome Research Institute of the National Institutes of Health.

*Correspondence to:
Dr. Raoul C. Hennekam, Department of Pediatrics, AMC, Meibergdreef 9, 1105AZ Amsterdam, Netherlands.
E-mail: r.c.hennekam@amc.uva.nl

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 3 October 2013
DOI 10.1002/ajmg.a.36249

METHODS

The present authors, all members of the Elements of Morphology group, used as source for the general terms the series of publications that previously defined these [Smith, 1975; Spranger et al., 1982; Opitz et al., 1987; Merks et al., 2003]. We selected terms that were still in use (for example we did not consider the term "anomalad" as the term was discontinued in 1987 [Opitz et al., 1987]). We divided the terms amongst the authors. Each prepared an overview of existing definitions of the term, a literature review, and a proposal for a new definition. The group convened at the National Institutes of Health in Bethesda on January 25–27, 2013 during which concept definitions were conceived. During a series of subsequent e-mail and telephone conferences, the definitions were refined. In May 2013 the definitions were forwarded to an international group of experts (Elements of Morphology Consortium; see appendix). During a second series of e-mail and telephone conferences, final definitions and comments were established.

If a term in the text is indicated in ***bold-italics***, that term is listed and a definition is available. The defined terms are illustrated in Fig. 1.

DEFINITIONS

Phenotype

Definition. All morphologic and functional attributes of an individual, or of the organs, tissues, or cells of that individual, except for the primary morphology of the genome.

Comment. The word phenotype is derived from the Greek φαινο (phaino) meaning "shining" or "showing" and *τύπος* (*tupos*) meaning "type." The phenotype encompasses all attributes of an individual, both at a cell or tissue level (e.g., physiology) and at the level of the individual (e.g., behavior or cognition). The definition excludes the primary morphology (i.e., DNA sequence structure) of the ***genotype*** as being part of the phenotype. Histone marks and epigenetic factors modifying the DNA sequence exist at the boundary of ***genotype*** and phenotype. Arguably, they can be considered a phenotype, as they can reflect the influence of metabolism and environment on an existing body component; alternatively they can reflect a heritable influence and be considered part of the genotype.

Genotype

Definition. The primary DNA sequence, either overall or at a specific locus, of an individual, or of the organ(s), tissue(s), or cell(s) of that individual.

Comment. Genotype includes both the nuclear and mitochondrial DNA sequence, and is the counterpart of the ***phenotype***. The term is used in two ways, both widely accepted: narrow (e.g., a patient's genotype is homozygous for a particular sequence variant) and broad (e.g., a patient's genotype explains the elevated risk for hypertension). Because of mosaicism the qualifier that a genotype may refer to part of the patient (organ; tissue; cell) was added.

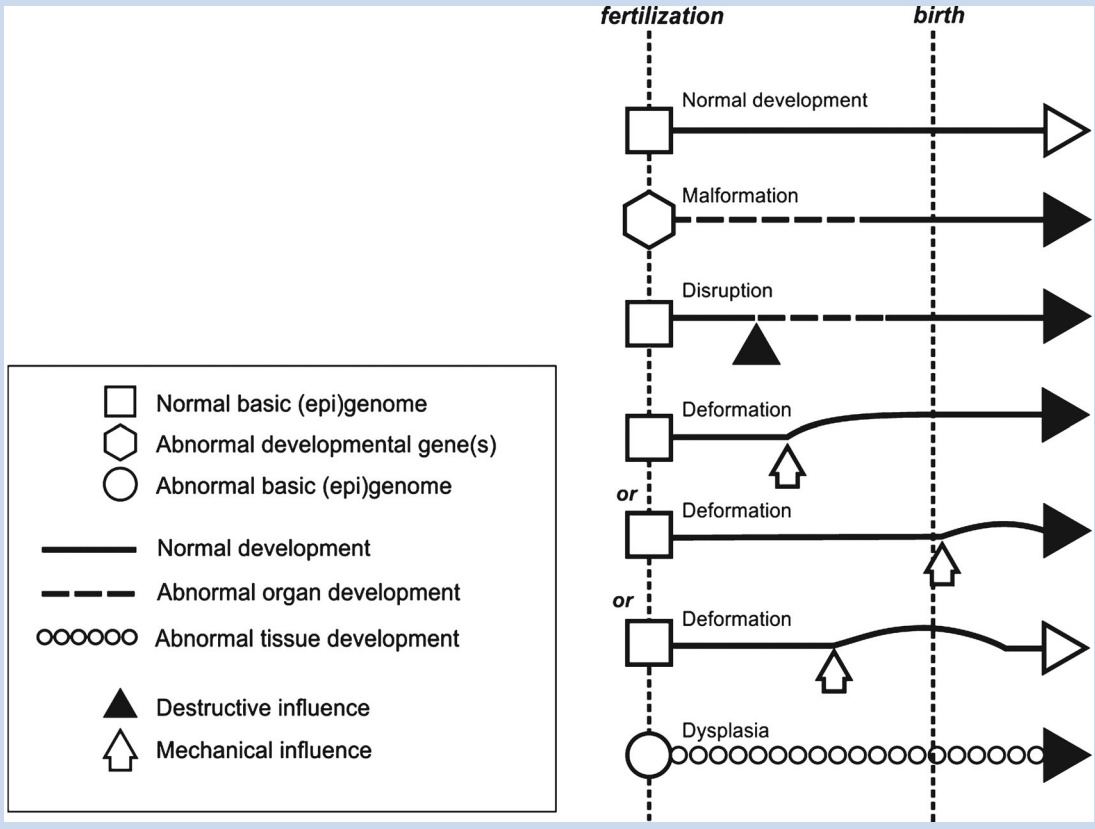

FIG. 1. Schematic representation of various types of morphologic anomalies compared to normal development.

Histone marks, transcription differences at an RNA level, and epigenetic factors modifying the DNA sequence, together with the genotype forming an individual's genome, exist at the boundary of genotype and ***phenotype***. Arguably, they can be considered a ***phenotype***, as they can reflect the influence of metabolism and environment on an existing body component; alternatively they can reflect a heritable influence and be considered part of the genotype.

Anomaly, Morphologic

Definition. An anatomic (microscopic and macroscopic) phenotype that represents a substantial departure from the appropriate reference population.

Subtypes. A ***major morphologic anomaly*** has a significant consequence for health or appearance at the time of evaluation, or had this in the past or will have it in the future. A ***minor morphologic anomaly*** has minimal, or no, health consequence but may have a modest impact on appearance.

Comment. The word is from the Greek ανωμαλος (an-omalos), which means "not normal." We use morphologic as a qualifier of anomaly to distinguish structural or anatomical attributes from physiologic attributes such as hypernatremia, which we consider abnormalities. We acknowledge that anomaly may be used in other contexts to describe functional or physiologic abnormalities with a different qualifier. We use "substantial departure" here to imply that a particular anomaly is found in a small fraction (typically <2.5%) of the population or, in the case of measurable anomalies, the measured sign falls outside the normal reference range for the population (> or <2 SD from the mean). A more liberal threshold (<4%) has been advocated by others [Marden et al., 1964; Merks et al., 2003]. Anomalies, either major or minor (including ***malformations***, ***deformations, disruptions, dysplasias***, and ***sequences***), can occur as isolated phenomena or as component manifestations of broader patterns or ***syndromes*** and are causally heterogeneous.

Some prior definitions of major and minor anomalies included additional criteria. For example, Marden et al. [1964] defined a major anomaly as having "an adverse effect on either the function or social acceptability of the individual" and a minor anomaly as one that is "neither of medical nor cosmetic consequence to the patient." The self-image and social acceptability of individuals with morphologic anomalies are complex psychological and social issues [Marik and Hoag, 2012; Masnari et al., 2012], which should be distinguished from the medical or biological description of the anomaly. Given the enormous variation in social and personal attitudes toward physical differences, we were hesitant to include such concepts in our definitions. For example, the wide use of cosmetic surgery in some cultures might lead to a number of minor anomalies being classified as major.

Replaces. Defect; birth defect; deviation; anatomical abnormality.

Variant, Morphologic

Definition. A mild anatomic phenotype that represents a small departure from the appropriate reference population.

Comment. Discontinuous (presence-absence) signs, such as an ear tag or a bifid uvula, are always ***anomalies***. Continuous (plus-minus) signs such as clinodactyly or hypermobile joints may be either variants or ***anomalies***. A variant is found in a small (typically between 2.5% and 10%) segment of the appropriate reference population justifying it to be an error of development. We acknowledge that in clinical genetics the term variant is also used to indicate a phenotype that resembles an entity but still differs from it, such as diastrophic dysplasia variant.

Malformation

Definition. A non-progressive, congenital morphologic anomaly of a single organ or body part due to an alteration of the primary developmental program.

Comment. The term malformation is derived from Latin words *malus* meaning "bad" or "wretched," and *formare* meaning "to form, to shape." Malformations typically arise during the embryonic period. The term malformation has been defined elsewhere to include both a phenotypic finding (as above) and the process of abnormal development (pathogenesis) [Spranger et al., 1982]. Since it is important to distinguish the process from the outcome, we have defined a malformation as the outcome. Although growth and other physiologic processes can affect the ***phenotype***, a malformation, like a ***disruption***, does not progress but is instead predominantly static. A malformation, like a ***deformation, disruption, dysplasia***, and ***sequence***, can occur as an isolated phenomenon or as a component manifestation of broader patterns, including ***syndromes***; malformations are therefore causally heterogeneous. The exact pathogenesis of human malformations is usually not understood but may be inferred from animal models. A malformation, like a ***dysplasia***, and as opposed to a ***deformation*** or ***disruption***, results from an intrinsic developmental process, which refers to the cellular and molecular pathways involved in organogenesis; the molecules in these pathways can be altered by gene mutations, teratogens, or combined effects. A malformation can be caused by a teratogen if the teratogen influences the intrinsic developmental process from the start. For example, limb anomalies are malformations if part of Holt–Oram syndrome and also malformations if part of thalidomide embryopathy, in which thalidomide inhibits the process of angiogenesis, which subsequently blocks the primary limb formation [Therapontosa et al., 2009]. But comparable limb defects in varicella embryopathy are ***disruptions***. We acknowledge the value of previous definitions of malformations that include the concept of alteration of a developmental field, indicating that a region of the embryo responds as a coordinated unit, both temporally and spatially [Opitz, 1983; Opitz, this issue].

Replaces. Birth defect, deformity.

Deformation

Definition. Altered shape or position of a body part due to aberrant mechanical force(s) that distorts an otherwise normal structure.

Comments. The word is derived from the Latin *de-formare*, equivalent to *de-*"departing from; reversing" and *formare* "to form, to shape." Deformations may result in loss of symmetry, altered alignment, abnormal position, or distorted configuration. A

morphologic anomaly caused by a normal force on an abnormal tissue has been termed a deformation, but this would more accurately be considered part of the dysplastic process. In some cases a deformation may be secondary to a dysplastic process, ***malformation***, etc. A deformation, like a ***malformation, disruption, dysplasia***, and ***sequence***, can occur as an isolated phenomenon or as a component manifestation of broader patterns, including ***syndromes***, Deformations are causally heterogeneous and may occur as a consequence of extrinsic or intrinsic mechanical force(s). Many structures are normally shaped, at least in part, by pressure or mechanical transduction, (e.g., palate, lungs) and some tissues undergo mechanical transduction during embryogenesis (e.g., neural tube, tendons, and joints).

Deformations can occur at any time in gestation or after birth, generally after organogenesis. Abnormal forces early in development may permanently alter structural relationships [Dunn, 1976]. When abnormal mechanical forces have been present over a prolonged period of time, a deformation may be more difficult to correct [Christianson et al., 1999; Flannery et al., 2012]. Deformations are usually reversible postnatally depending on how longstanding they are and how much growth has occurred subsequent to the initial compressive forces [Graham et al., 1979; Graham, 1988; Van Allen et al., 1994; Levine et al., 1996]. We and others [Graham et al., 1980; Pollack et al., 1997] have found that early treatment of deformations can improve final outcome but there is a small window for such treatment to be successful. The term "deformity" should not be used as a synonym for deformation or ***malformation*** since it is not a synonym, and its use is confusing as to the original mechanism and it may be regarded as pejorative.

Replaces. Deformity.

Disruption

Definition. A non-progressive, congenital morphologic anomaly due to the breakdown of a body structure that had a normal developmental potential.

Comment. Disruption literally means to break apart from the Latin words *dis* indicating "apart; removal" and *rumpere* meaning "tear down." The term refers to the "breaking apart" of body structures that are otherwise developing normally. It is a term usually used to describe events happening *in utero*. The timing and nature of the disruptive event will determine the subsequent consequences and may result in perturbation of normal growth and development and destruction of existing tissue. A disruption, like a ***malformation, deformation, dysplasia***, and ***sequence***, can occur as an isolated phenomenon or as a component manifestation of broader patterns, including ***syndromes***; disruptions are causally heterogeneous. An early disruption can result in a secondary ***malformation*** or be an initial event of a ***sequence***.

There are many potential origins of disruption including vascular, infectious, teratogenic, and mechanical. Disruption can affect several tissue types in a well-demarcated anatomical region and the phenotypic abnormalities may not conform to the boundaries normally imposed by embryonic development [Merks et al., 2003]. For example, interruption of the regional blood supply to a developing limb leads to ischemia, necrosis, and sloughing of the body part during development resulting in structural damage. Fetal aminopterin/methotrexate toxicity can cause limb defects secondary to disruption although, as with other teratogens, and depending on the timing of exposure, it can also cause ***malformations*** [Corona-Rivera et al., 2010]. In identical twins, the *in utero* death of one twin can result in severe disruption events in the other due to the circulation of necrotic products [Zankl et al., 2004]. Some abnormal developmental processes can cause both a disruption and a ***deformation***. For example, constriction rings at the tip of a finger associated with bands (fibrous strands of tissue) are often used as an example of disruption but fibrous bands can also cause ***deformation*** depending on the timing and extent of the band formation and the constraint on tissues caused by the banding process. Of note, disruption events should be distinguished from normal developmental programming, such as the normal programmed cell death (apoptosis) of tissue within the developing limbs [Towers and Tickle, 2009] and the hindgut [Qi et al., 2000]. These will only be of relevance clinically if the process fails to occur or occurs to excess.

Dysplasia

Definition. A morphologic anomaly arising either prenatally or postnatally from dynamic or ongoing alteration of cellular constitution, tissue organization or function within a specific organ or a specific tissue type.

Comments. The term dysplasia is derived from the Greek δνσ (dys) meaning 'bad' and πλαασω (plaso) meaning "to form." Since the defect may involve all of the anatomic sites in which the affected tissue element is present, there can be widespread involvement, which is not confined to a single organ. Alternately, dysplasia may be localized, with the abnormal element occupying part of an organ [Spranger et al., 1982]. Since the tissue itself is intrinsically abnormal, the clinical impact may persist or worsen as long as that tissue continues to grow or function. This contrast with other pathogenetic mechanisms, such as ***malformation***, ***deformation***, and ***disruption***, where the causative actions are often relatively brief in duration and occur during a distinct interval of development [Aase, 1990]. Dysplastic tissues may not respond to normal mechanical pressures in a normal way (e.g., bowing in chondrodysplasias), but this should be considered part of the dysplastic process and not as a ***deformation***. A dysplasia, like a ***malformation, deformation, disruption***, and ***sequence***, can occur as an isolated phenomenon or as a component manifestation of broader patterns, including ***syndromes***. Dysplasias are causally heterogeneous: they may be genetic (Mendelian, multifactorial, or aneuploidy); or secondary to teratogenic exposure (e.g., diethylstilbestrol and vaginal dystopic adenosis). Dysplasias may be: metabolic in nature (hypophosphatasia); involve one germ layer (ectodermal dysplasia) or multiple germ layers; be limited to a single organ system (bone in skeletal dysplasia), be generalized affecting several systems (connective tissue disorder), or localized (presacral teratoma); unilateral (acoustic neuroma), paired (for bilateral organs), multiple (affecting all elements of a system like vertebra in platyspondyly) or multifocal (affecting multiple local areas as in angiomatosis); benign or pre-malignant (colon polyp); static (hairy pigmented nevus), progressive (neurofibromatosis) or evanescent (strawberry hemangioma); prenatal (presacral teratoma) or postnatal (testicular teratoma) [Spranger et al., 1982]. As noted above, tumorigenesis

is a dysplastic process and all cancers could be considered dysplasias. We recognize that certain ***anomalies*** that have historically been designated as dysplasias are in fact malformations and the opposite is also true (Table I). Also, a single cause may lead to both dysplasia and ***malformation***, for example, Ectrodactyly–Ectodermal dysplasia–Clefting syndrome or Goltz–Gorlin syndrome.

Synonym. Abnormal histiogenesis.

Syndrome

Definition. A pattern of anomalies, at least one of which is morphologic, known or thought to be causally (etiologically) related.

Comments. The word syndrome is derived from the Greek words *σύν* (syn), which means "together" and *δρόμος* (dromos) meaning "running." The term syndrome is used by other medical disciplines when only functional abnormalities are present, for example, nephrotic syndrome or Landau–Kleffner syndrome. We recognize that the term is used in a less restrictive way by both medical and non-medical disciplines [Spranger, 2013] but for Dysmorphology we have restricted our definition of the term to entities that include ***morphologic anomalies***. We have limited the use of the term syndrome to patterns of anomalies that are causally related but which are not necessarily pathogenetically related. We acknowledge that identifying families or communities of overlapping but still distinct syndromes, that are caused by mutations in the same gene or by genes working in the same pathway or network, can be very helpful for patient care and research alike [Pinsky, 1974; Brunner and van Driel, 2004]. Examples are the ciliopathies [Davis and Katsanis, 2012], rasopathies [Tidyman and Rauen, 2009], and laminopathies [Worman, 2012].

The co-occurrence of two anomalies by chance is specifically excluded by the present definition. This has been termed 'false syndrome' [Cohen, 1989]. The rapid increase in use of Next Generation Sequencing techniques will allow more frequent detection of such co-occurrences.

Clinically, we define the scope of a syndrome based on the major characteristics of the entity. These can be major or minor ***anomalies*** and functional abnormalities, such as those affecting neurological, cognitive, sensory or behavioral functioning. ***Anomalies*** that characterize a syndrome can be ***malformations, deformations*** (e.g., the broadening of the mandible due to continuous pressure by the large tongue in Beckwith-Wiedemann syndrome), ***disruptions*** (e.g., the distal limb anomalies in Adams-Oliver syndrome), ***sequences*** (e.g., the decreased mobility in joints in restrictive dermopathy) or ***dysplasias*** (e.g., the ectodermal dysplasia in ectrodactyly ectodermal dysplasia—clefting syndrome).

Replaces. Spectrum.

Sequence

Definition. One or more secondary morphologic anomalies known or presumed to cascade from a single malformation, disruption, dysplasia, or deformation.

Comments. The word is derived from the Latin *sequentia*, which is derived from *sequi*, which means "to follow." A sequence is a mechanistic process comprising a series of events that are the consequence of an ***anomaly*** [Smith, 1975]. The downstream ***anomalies*** are not themselves attributed directly to the primary cause (etiology), such as a mutated gene. This definition distinguishes sequence from ***syndrome*** because in a ***syndrome***, the multiple ***anomalies*** are caused directly and independently by the underlying etiologic abnormality, for example, trisomy 21. A sequence, like a ***malformation, deformation, disruption,*** and ***dysplasia***, can occur as an isolated phenomenon or as a component manifestation of broader patterns, including ***syndromes***; and again, like ***malformations*** are causally heterogeneous.

An example of a sequence is the Pierre Robin sequence, in which a small mandible (which is itself of heterogeneous causation) is presumed to lead to a heaped and protruding tongue, which in turn interferes with palatal shelf closure, leading to a cleft palate. A ***syndrome*** may include a sequence, for example, the TARP (Talipes equinovarus, Atrial septal defect, Robin sequence, and Persistent left superior vena cava) syndrome, which includes the Pierre Robin sequence [Gorlin et al., 1970; Kurpinski et al., 2003]. In addition, TARP also has the individual ***anomalies*** of left superior vena cava, atrial septal defects and talipes equinovarus, which are presumably caused directly by the pleiotropic effects of the mutated *RBM10* gene [Johnston et al., 2010].

One of the challenges when defining and describing a sequence is to distinguish and describe the order of primary, secondary, or tertiary effects. For instance, fetal akinesia (secondary) may be

TABLE I. Problematic Names in Entities, and Suggested Alternatives Based on Presently Proposed Nomenclature

Entity	OMIM	Suggested alternative
Adams–Oliver syndrome	100300	Adams–Oliver dysplasia
Bruck syndrome	259450	Bruck dysplasia
Cowden syndrome type	158350	Cowden dysplasia/multiple hamartoma, Cowden type
Cranioectodermal dysplasia	218330	Sensenbrenner syndrome
Frontonasal dysplasia	136760	Frontonasal malformation/Frontonasal syndrome
Hutchinson–Gilford syndrome	176670	Progeria, Hutchinson–Gilford type/Hutchinson–Gilford dysplasia
Marden–Walker syndrome	248700	Marden–Walker sequence
Marfan syndrome	154700	Marfan dysplasia
Pena-Shokeir syndrome type I	208150	Fetal hypokinesia sequence
Potter syndrome	191830	Potter sequence

caused by primary abnormalities of muscle, nerve, endplate, bone, joint, tendon, teratogenic agents, maternal/illness and/or space occupying factors, and may itself lead to tertiary morphologic ***anomalies***. Subsequently, fetal akinesia may lead to pulmonary hypoplasia due to lack of amniotic fluid and/or due to lack of fetal diaphragm movements and subsequent decrease in expansion of the lungs. Pulmonary hypoplasia may then lead to a chest shape abnormality.

Replaces. Anomalad, Complex, Cascade [Spranger et al., 1982].

Association

Definition. A pattern of anomalies, at least two of which are morphologic, that occur together more often than would be expected by chance, and where a causal relationship has not been identified.

Comment. The word is derived from the Latin *associare*, which is the combination of the word *ad* "to" and the word *sociare* meaning "make an ally." This term may not be durable, as what are now considered single associations, may be separated into multiple, distinct ***syndromic*** entities. We are uncertain that the term warrants inclusion here, but decided that its current usage makes a definition worthwhile. For example, the notion of an association can be practically useful for motivating clinicians to evaluate patients with associations for other related ***anomalies*** that may be unappreciated but important for health. Further, such investigation can assist in the development of a differential diagnosis. Most associations are heterogeneous, probably comprising multiple ***syndromes*** with overlapping features, and for this reason no unitary underlying causal basis is apparent.

There are relatively few associations; VACTERL/VATER (Vertebral malformations, Anal atresia or stenosis, Cardiac defects, Tracheo-Esophageal fistula, Radial defects, Renal anomalies, and non-radial Limb defects) [Solomon, 2011] and MURCS (MUllerian anomalies, Renal aplasia, Cervical thoracic Somite anomaly) [Braun-Quentin et al., 1996] are the two that this group currently recognizes. Historically, a number of associations have been found to be ***syndromes***, the best example being the former CHARGE association [Sanlaville and Verloes, 2007]. Once the causative gene was identified [Vissers et al., 2004], was changed to CHARGE syndrome. We anticipate that this will happen for most, if not all, associations.

DISCUSSION

The present series of definitions is part of an iterative process following on several earlier definitions of these general terms [Smith, 1975; Spranger et al., 1982; Opitz et al., 1987]. We concluded that updating the terms was necessary due to recent advances in our understanding of molecular genetics and human development. We are pleased to receive feedback.

The need for an update is illustrated by the term syndrome. Each of the earlier definitions required a single unifying cause for the malformations within a syndrome. When earlier definitions were formulated, it was expected that further developments in molecular genetic research and diagnostics would identify the monogenic cause; the presumption being that genes would map to phenotypes in a one-to-one correspondence. We have now learned, a mutation in a single gene can cause multiple distinct entities, a single phenotype can be caused by mutations in one of a number of genes, and variations in the phenotype caused by a mutation in a single gene are larger than expected [Hennekam, 2007]. Indeed, disorders that can be completely explained by a mutation in a single gene ("truly monogenic disorders") do not seem to exist [Hennekam and Biesecker, 2012]; the effect of the primary locus is substantially influenced by sequence variants elsewhere in the genome [Slavotinek and Biesecker, 2003], epigenetic phenomena such as imprinting [Rando, 2012], topologic attributes of chromosomes [Cremer et al., 2006], and so on. Therefore, it is no longer appropriate to require "a single cause" for the definition of a syndrome. We anticipate that additional future insights will lead to further evolution of the definitions.

We acknowledge it may be difficult or impossible to categorize a phenotype at initial physical exam. One may need additional information about the family of the investigated individual, the population from which s/he originates, and information about the most likely pathogenesis, either from literature or by further investigations of the affected individual. An example is ectrodactyly—ectodermal dysplasia-clefting (EEC) syndrome: is this truly a syndrome or can all signs and symptoms be explained as part of a dysplasia? Only recently, after detailed animal studies, has it become likely that the ectrodactyly component can be considered a consequence of dysplasia of the apical dermal ridge, while the clefting should be considered a malformation (Dr. Hans van Bokhoven, personal communication 2013). EEC syndrome can therefore indeed be classified as a syndrome. We acknowledge that categorization of entities may need corrections over time as our insights in etiology and pathogenesis of anomalies improves.

While we define here the term syndrome in general, we do not specify how individual syndromes should be named. For example, it is not possible to represent in the name of a syndrome both the complete phenotype and all relevant factors of its causation. Systems that use multiple axes for the phenotype, cause, and genetic and environmental modifiers have been proposed [Cohen and Maclean, 1999; Robin and Biesecker, 2001]. Despite the thoughtful design of these systems, they have not found practical application, in part because of their complexity. We realize some existing names for disorders are not correct (for instance Marfan syndrome should be called Marfan dysplasia) but these can be difficult to change in general use. The lumping and splitting of syndromes, that is, whether or not to distinguish two phenotypes, which show significant resemblance as variations of a single entity or as two separate entities, remains contentious [Hennekam, 2007]. We acknowledge that the naming and designation of syndromes and anomalies is challenging and a full discussion of all aspects is needed, but this is outside the scope of the present paper. We suggest that it would be useful to convene an international working group and a permanent committee for the naming of syndromes, similar to existing nomenclature groups for cytogenetics (International Standard of Cytogenetic Nomenclature) and molecular genetics (Human Genome Variation Society nomenclature recommendations).

ACKNOWLEDGMENTS

LGB is supported by funding from the Intramural Research Program of the National Human Genome Research Institute of the National Institutes of Health.

REFERENCES

Aase JM. 1990. Principles of normal and abnormal embryogenesis. In: Diagnostic dysmorphology. New York and London: Plenum Medical Book Company. pp 5–13.

Allanson JE, Biesecker LG, Carey JC, Hennekam RC. 2009a. Elements of morphology: Introduction. Am J Med Genet A 149A:2–5.

Allanson JE, Cunniff C, Hoyme HE, McGaughran J, Muenke M, Neri G. 2009b. Elements of morphology: Standard terminology for the head and face. Am J Med Genet A 149A:6–28.

Biesecker LG, Aase JM, Clericuzio C, Gurrieri F, Temple K, Toriello H. 2009. Elements of morphology: Standard terminology for the hands and feet. Am J Med Genet A 149A:93–127.

Braun-Quentin C, Billes C, Bowing B, Kotzot D. 1996. MURCS association: Case report and review. J Med Genet 33:618–620.

Brunner HG, van Driel MA. 2004. From syndrome families to functional genomics. Nat Rev Genet 5:545–551.

Carey JC, Cohen MM Jr, Curry CJ, Devriendt K, Holmes LB, Verloes A. 2009. Elements of morphology: Standard terminology for the lips, mouth and oral region. Am J Med Genet A 149A:77–92.

Carey JC. 2011. The clinical delineation of malformation syndromes: Historical prospective and future direction. Am J Med Genet A 155A: 2066–2068.

Christianson C, Huff D, McPherson E. 1999. Limb deformations in oligohydramnios sequence: Effects of gestational age and duration of oligohydramnios. Am J Med Genet 86:430–433.

Cohen MM Jr. 1989. Syndromology: An update conceptual overview. I. Syndrome concepts, designations, and population characteristics. Int J Oral Maxillofac Surg 18:216–222.

Cohen MM Jr, Maclean RE. 1999. Should syndromes be defined phenotypically or molecularly? Resolution of the dilemma. Am J Med Genet 86:203–204.

Corona-Rivera JR, Rea-Rosas A, Santana-Ramirez A, Acosta-Leon J, Hernandez-Rocha J, Miquel-Jimenez K. 2010. Holoprosencephaly and genitourinary anomalies in fetal methotrexate syndrome. Am J Med Genet A 152A:1741–1746.

Cremer T, Cremer M, Dietzel S, Müller S, Solovei I, Fakan S. 2006. Chromosome territories—A functional nuclear landscape. Curr Opin Cell Biol 18:307–316.

Davis EE, Katsanis N. 2012. The ciliopathies: A transitional model into systems biology of human genetic disease. Curr Opin Genet Dev 22:290–303.

Dunn PM. 1976. Congenital postural deformities. Br Med Bull 32:71–76.

Flannery AB, Looman WS, Kemper K. 2012. Evidence-based care of the child with deformational plagiocephaly, part II: Management. J Pediatr Health Care 26:320–331.

Gorlin RJ, Cervenka J, Anderson RC, Sauk JJ, Bevis WD. 1970. Robin's syndrome. A probably X-linked recessive subvariety exhibiting persistence of left superior vena cava and atrial septal defect. Am J Dis Child 119:176–178.

Graham JM Jr. 1988. Smith's recognizable patterns of human deformation. 2nd edition. Philadelphia, PA: WB Saunders Co.

Graham JM Jr, Badura RJ, Smith DW. 1980. Coronal craniostenosis: Fetal head constraint as one possible cause. Pediatrics 65:995–999.

Graham JM Jr, deSaxe M, Smith DW. 1979. Sagittal craniostenosis: Fetal head constraint as one possible cause. J Pediatr 95:747–750.

Hall BD, Graham JM Jr, Cassidy SB, Opitz JM. 2009. Elements of morphology: Standard terminology for the periorbital area. Am J Med Genet A 149A:29–39.

Hennekam RC. 2007. What to call a syndrome? Am J Med Genet A 143A: 1021–1024.

Hennekam RC, Allanson JE, Biesecker LG, Carey JC, Opitz JM, Vilain E. 2013. Elements of morphology: Standard terminology for the external genitalia. Am J Med Genet A 161A:1238–1263.

Hennekam RC, Cormier-Daire V, Hall JG, Méhes K, Patton M, Stevenson RE. 2009. Elements of morphology: Standard terminology for the nose and philtrum. Am J Med Genet A 149A:61–76.

Hennekam RC, Biesecker LG. 2012. Next-generation sequencing demands next-generation phenotyping. Hum Mutat 33:884–886.

Hunter A, Frias J, Gillessen-Kaesbach G, Hughes H, Jones K, Wilson L. 2009. Elements of morphology: Standard terminology for the ear. Am J Med Genet A 149A:40–60.

Johnston JJ, Teer JK, Cherukuri PF, Hansen NF, Loftus SK, Chong K, Mullikin JC, Biesecker LG. 2010. Massively parallel sequencing of exons on the X chromosome identifies RBM10 as the gene that causes a syndromic form of cleft palate. Am J Hum Genet 86:743–748.

Kurpinski KT, Magyari PA, Gorlin RJ, Ng D, Biesecker LG. 2003. Designation of the TARP syndrome and linkage to Xp11.23-q13.3 without samples from affected patients. Am J Med Genet A 120A:1–4.

Levine D, Kilpatrick S, Damato N, Callen PW. 1996. Dolichocephaly and oligohydramnios in preterm premature rupture of the membranes. J Ultrasound Med 15:375–379.

Marden PM, Smith DW, McDonald MJ. 1964. Congenital anomalies in the newborn infant, including minor variants. J Pediatr 64:357–371.

Marik PK, Hoag JA. 2012. Self-concept in youth with congenital facial differences: Development and recommendations for medical providers. Pediatr Dermatol 29:549–554.

Masnari O, Landolt MA, Roessler J, Weingaertner SK, Neuhaus K, Meuli M, Schiestl C. 2012. Self- and parent-perceived stigmatisation in children and adolescents with congenital or acquired facial differences. J Plast Reconstr Aesthet Surg 65:1664–1670.

Merks JHM, van Karnebeek CD, Caron HN, Hennekam RC. 2003. Phenotypic abnormalities: Terminology and classification. Am J Med Genet A 123A:211–230.

Opitz JM. 1983. The developmental field concept in clinical genetics. J Pediatr 101:805–809.

Opitz JM, Czeizel A, Evans JA, Hall JG, Lubinsky MS, Spranger JW. 1987. Nosologic grouping in birth defects. In: Vogel F, Sperling K, editors. Proceedings of the VII international congress of human genetics. Berlin, Heidelberg: Springer-Verlag. pp 382–385.

Pinsky L. 1974. A community of human malformation syndromes involving the Mullerian ducts, distal extremities, urinary tract, and ears. Teratology 9:65–79.

Pollack IF, Losken HW, Fasick P. 1997. Diagnosis and management of posterior plagiocephaly. Pediatrics 99:180–185.

Qi BQ, Beasley SW, Williams AK, Fizelle F. 2000. Apoptosis during regression of the tailgut and septation of the cloaca. J Pediatr Surg 35:1556–1561.

Rando OJ. 2012. Daddy issues: Paternal effects on phenotype. Cell 151: 702–708.

Robin NH, Biesecker LG. 2001. Considerations for a multiaxis nomenclature system for medical genetics. Genet Med 3:290–293.

Sanlaville D, Verloes A. 2007. CHARGE syndrome: An update. Eur J Hum Genet 15:389–399.

Slavotinek A, Biesecker LG. 2003. Genetic modifiers in human development and malformation syndromes, including chaperone proteins. Hum Mol Genet 12(S1):R45–R50.

Smith DW. 1975. Classification and nomenclature and naming of morphological defects. J Pediatr 87:162–164.

Smith DW. 1979. Commentary: Redundant skin folds in the infant–their origin and relevance. J Pediatr 94:1021–1022.

Solomon BD. 2011. VACTERL/VATER association. Orphanet J Rare Dis 6:56.

Spranger J. 2013. Syndromes A, syndromes B, syndromes C. Am J Med Genet A 161A:228–229.

Spranger J, Benirschke K, Hall JG, Lenz W, Lowry RB, Opitz JM, Pinsky L, Schwarzacher HG, Smith DW. 1982. Errors of morphogenesis: Concepts and terms. Recommendations of an International Working Group. J Pediatr 100:160–165.

Therapontosa C, Erskineb L, Gardnerc ER, Figgd WD, Vargesson N. 2009. Proc Natl Acad Sci 106:8573–8578.

Tidyman WE, Rauen KA. 2009. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 19:230–236.

Towers M, Tickle C. 2009. Growing models of vertebrate limb development. Development 136:179–190.

Van Allen MI, Brown ZA, Plovie B, Hanson ML, Knopp RH. 1994. Deformations in infants of diabetic and control pregnancies. Am J Med Genet 53:210–215.

Vissers LE, Van Ravenswaaij CM, Admiraal R, Hurst J, De Vries B, Jansen I, Van der Vliet W, Huys E, De Jong P, Hamel B, Schoenmakers E, Brunner H, Veltman J, Van Kessel A. 2004. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957.

Worman HJ. 2012. Nuclear lamins and laminopathies. J Pathol 226:316–325.

Zankl A, Brooks D, Boltshauser E, Largo R, Schinzel A. 2004. Natural history of twin disruption sequence. Am J Med Genet 127A:133–138.

APPENDIX

Elements of Morphology Consortium. Members of the consortium are Judith Allanson (Ottawa), Leslie Biesecker (Bethesda), John Carey (Salt Lake City), Suzanne Cassidy (San Francisco), Claire Clericuzio (Albuquerque), Chris Cunniff (Tucson), Helen Firth (Cambridge), Judith Hall (Vancouver), Raoul Hennekam (Amsterdam), Alasdair Hunter (Ottawa), Kenjiro Kosaki (Tokyo), Pablo Lapunzina (Madrid), Angela Lin (Boston), Giovanni Neri (Rome), John Opitz (Salt Lake City), Stephen Robertson (Dunedin), Jurgen Spranger (Mainz), Constance Stumpel (Maastricht), Karen Temple (Southampton), Helga Toriello (Grand Rapids), Alain Verloes (Paris), and Sue White (Melbourne).