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Phenotypic Abnormalities:
Terminology and Classification

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Clinical morphology has proved essential for the successful delineation of hundreds of syndromes and as a powerful instrument for detecting (candidate) genes (Gorlin et al. [2001]; Syndromes of the Head and Neck; Oxford: Oxford University Press. 1 p]. The major approach to reach this has been careful clinical evaluations of patients, focused on congenital anomalies. A similar careful physical examination performed in patients, who have been treated for childhood cancer, may allow detection of concurrent patterns of anomalies and provide clues for causative genes. In the past, several studies were performed describing the prevalence of anomalies in patients with cancer. However, in most studies, it was not possible to indicate the biologic relevance of the recorded anomalies, or to judge their relative importance. Are the detected anomalies common variants, and should they thus be regarded as normal, or are they minor anomalies or true abnormalities, indicating a possible developmental cause? Classification of items in the categories of common variants (disturbances of phenogenesis with a prevalence >4%), minor anomalies (disturbances of phenogenesis with a prevalence ≤4%), and malformations (disturbances of embryogenesis) should allow weighing the importance of the scored items in the population under study, and should facilitate assessment of developmental disturbances (if any) in a study group. The lack of published consensus in the literature led us to produce a classification list with a twofold goal. First, we wanted to enhance uniformity in the scoring and classification of apparently abnormal physical findings by a nomenclature for errors of morphogenesis detectable on surface examination, and secondly a uniform classification system. This should allow investigators to evaluate systematically the presence of patterns in phenotypic anomalies, in the general population, and in patients with various disorders, suspected to be a developmental anomaly. Also, normal values may be obtained this way. Second, the list will allow a determination of the importance of the collected symptoms in a study population. We tested the feasibility of the application of the classification list in a study population: the list was piloted in a group of patients who have had cancer as a child, to detect patterns of anomalies related to specific types of tumors. © 2003 Wiley-Liss, Inc.

KEY WORDS: phenotypic abnormalities; terminology; classification; pediatric cancer; congenital; abnormality; minor anomaly; normal variant; embryogenesis; phenogenesis; deformity; disruption; dysplasia; clinical morphology

INTRODUCTION

Terminology

Prior to the study, it was paramount to set definitions of all manifestations. Aase [1990a] subdivided all items into two categories: abnormalities and minor variants. Abnormalities were further subdivided in malformations, deformations, disruptions, and dysplasias according to their suspected cause [Spranger et al., 1982]. Minor variants were subdivided in two categories, minor anomalies and common variants, based upon their implication and prevalence.

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Abnormalities

A malformation was defined as a disturbance of embryogenesis (morphogenesis) [Opitz, 1985], and was classified as "mild" if it had little effect on normal functioning of the affected individual. All other malformations were called major malformations. Examples of mild malformations are ear pits and supernumerary nipples. Malformations are, by definition, results of early events, which are often oligogenic (although they can also be polygenic), leading to qualitatively different developmental endproducts within the individual. As the threshold principle is frequently involved in morphogenesis, defects in this process lead to all-or-none traits [Opitz, 1985]. Although malformations may be mild and have little or no effect on the functioning of the individual, they are always abnormal.

Deformations are produced by aberrant mechanical forces that distort otherwise normal structures, resulting from maternal or fetal factors, occurring at any time in gestation.

Disruptions are structural defects caused by interference with the development of genetically normal primordia, resulting from destructive events, caused by problems of various origin (for instance of vascular, infectious, or mechanical origin), commonly affecting several tissue types in a well-demarcated anatomic region; the structural damage does not conform to the boundaries normally imposed by embryonic development.

The term dysplasia refers to abnormal histogenesis or function of a specific tissue type, which can be focal or distributed throughout the body, resulting in clinically apparent structural changes, which have a continuing course. Since the tissue itself is intrinsically abnormal, the effect on the clinical symptom may persist or worsen as long as the tissue continues to grow or function. In this way, dysplasias differ from the other three categories, where the actions causing it are relatively brief in duration [Aase, 1990a].

Minor Variants

Aase subdivided minor variants into two categories, minor anomalies and spectrum variants [Aase, 1990b]. Minor congenital anomalies have been widely discussed. Frías and Carey [1996] described the history of the definitions used in the major studies performed. Marden et al. [1964] arbitrarily divided congenital anomalies into two categories according to their severity: Major anomalies have an adverse effect on either function or social acceptability of the individual, while minor anomalies are not of medical or cosmetic consequence to the patient. Anomalies observed in more than 4% of infants were considered normal phenotypic variants. Hook [1971] used the same definitions, referring to minor congenital anomalies as morphological anatomical variations. Méhes [1983] followed the nomenclature set by Marden et al. [1964], pointing out that many apparent minor anomalies represent extreme normal variants rather than true birth defects. However, their frequency is much higher in subjects with congenital disorders, the latter being confirmed by other groups [Marden et al., 1964; Hook, 1971; Leppig et al., 1987]. Merlob et al. [1985] divided minor abnormalities into three groups: (1) minor congenital malformations, anatomic defects due to errors of organogenesis, not being of medical significance; (2) minor variants, phenotypic variations, not present in multiple congenital anomaly syndromes, often present in the family or the patient's ethnic group; and (3) transient developmental disorders, minor defects in embryonic development which disappear by themselves. Opitz [1985] divided the so-called minor congenital anomalies into two categories primarily based on the particular phase in which the developmental abnormality occurred: (1) mild malformations, which arise during embryogenesis, and should always be considered malformations, whether primary or secondary; (2) minor anomalies, which are defects of phenogenesis, arising during fetal or early postnatal life. Opitz further specified a minor anomaly as a polygenic event, in contrast to mild malformations. Defects in phenogenesis lead to quantitative differences between individuals; phenogenesis represents a process of developmental fine-tuning. It does not involve threshold decisions but only shades of differences [Opitz, 1985]. In their review, Frías and Carey [1996] conclude by complimenting Merlob [1994] for introducing the term mild errors of morphogenesis (MEM) as "an excellent substitute for minor congenital anomalies" in as much as MEM encompasses both the errors of organogenesis, including mild malformations, disruptions, and dysplasias, and the errors of phenogenesis, or minor anomalies. However, for studies like ours, describing patterns of anomalies in a specific study population, searching for a possible developmental etiology in the specific patient group, abnormalities of organogenesis and phenogenesis should not be covered by a single term such as "mild errors of morphogenesis." In order to assign the appropriate weight to the findings scored in a population, defects of organogenesis and phenogenesis should be classified as two separate categories: (1) malformations, either mild or major, representing defects of organogenesis and (2) minor variants, either common variants or minor anomalies, representing defects of phenogenesis.

Two factors discriminate minor anomalies from common (or phenotypic) variants: prevalence and implication. In larger scale studies, minor anomalies appeared to have a prevalence of 4% or lower [Marden et al., 1964; Méhes, 1983; Leppig et al., 1987]. Therefore, deviations of phenogenesis with an expected prevalence in the normal population above 4% are called, by definition, normal phenotypic variants. The presence of multiple minor anomalies should alert the attending physician for the prevalence of a major malformation: all four (newborn) population studies on minor anomalies showed that the presence of three or more minor anomalies in a newborn makes the neonate more likely to have a major malformation, the likelihood ranging in the different studies from 19.6 to 90% [Marden et al., 1964; Méhes, 1983; Merlob et al., 1985; Leppig et al., 1987]. Multiple minor anomalies may imply an effect of aneuploidy [Opitz, 1985].

Normal Values

Until now, large-scale studies on the prevalence of minor anomalies have been performed in newborn infants only [Marden et al., 1964; Méhes, 1983; Merlob et al., 1985; Leppig et al., 1987]. As changes in anomalies occur with growth, and the detection rate may be different at different ages [Myrianthopoulos and Chung, 1974; Méhes, 1977], these prevalence figures may not be correct in other age groups. This makes it more difficult to predict which of these should be tagged as minor anomaly in older children and adults. Based on our mutual clinical experience in older children and adults, we selected a number of anomalies of which we expected the prevalence in the normal population of older children and adults to be 4% or below, and tagged these minor anomalies. All other minor variants were expected to have a prevalence of more than 4% and were registered as common variants.

Summary

The classification of physical anomalies as proposed in our list is based on the following principle. According to their (suspected) pathogenesis, all anomalies are subdivided in two main categories (depicted in Fig. 1): (1) abnormalities and (2) minor variants, of which the former more strongly suggest abnormal pre- or postnatal development. According to their suspected pathogenesis, abnormalities are subdivided into "A" malformations and "B" deformations, disruptions, dysplasias, and other abnormalities, the latter being secondary to abnormal morphogenesis and/or function of other important structures and which cannot be classified as deformations, disruptions, or dysplasias. Minor variants, deviations of phenogenesis, are subdivided into two categories, based on their prevalence and implication: (1) minor anomalies having an expected prevalence in the general population of $\leq$4% and generally indicating a possible genetic defect and (2) common variants having a prevalence of >4% in the normal population.

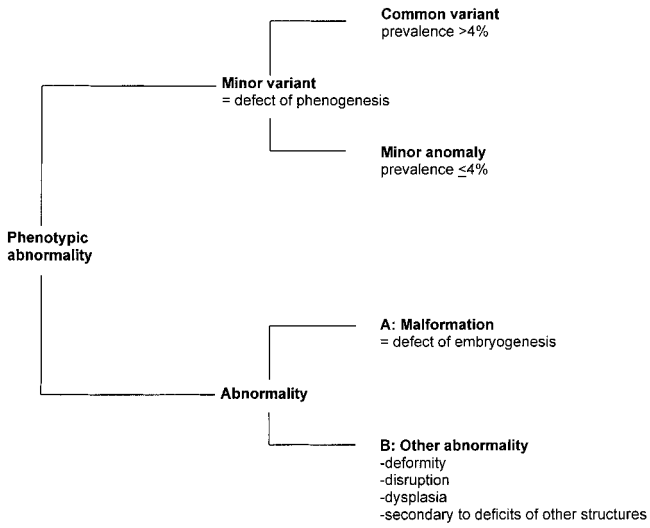

Fig. 1. Schematic depiction of the terminology and classification system of phenotypic abnormalities.

METHODS

In selecting the abnormal physical findings for definition and classification, we used two sources: Aase's text on dysmorphology which provides definitions of minor and major anomalies [Aase, 1990b], and the London Dysmorphology DataBase (LDDB) [Winter and Baraitser, 2001] which is nowadays the most commonly used database providing an overview and definitions of anomalies. From both sources, we selected all anomalies, which can be evaluated during surface examination by a physician trained in clinical morphology. Functional symptoms (e.g., lactorrhea) were not scored, as abnormal functioning may well be the result of a disturbed physiological process, rather than of an abnormal organogenesis or phenogenesis. The indexes of all 2000–2002 issues of this journal were scanned for possible missing items; those were added to the list.

Using the LDDB as a model, a tree was built with 29 major areas defined by either anatomy or function, 5 areas less than the total of 34 in the LDDB, as in our study, only findings picked up by surface examination can be scored, making the headings "urinary system," "blood vessels," "endocrine," "hematology/immunology," and "skeletal" inappropriate for our list. As in the LDDB, the 29 major areas were further subdivided into a total of 98 smaller areas, which were finally divided into a total of 683 single anomalies, describing all individual abnormalities and minor variants that can be scored by surface examination.

We classified the physical findings in the earlier described categories. However, the same abnormality can be classified in different subgroups according to its cause: for example, absence of a finger may be the result in one child of intrauterine vascular dysfunction, as has been suggested in Adams–Oliver syndrome and fetal thalidomide syndrome, and should then be scored as a disruption, while the same absence in a child with oral-facial-digital syndrome should be scored as a malformation. Since sub-classification of anomalies according to pathogenesis was often only possible after careful individual evaluation, which was not the goal of our (population) study, we decided to use the term abnormalities as defined by Aase. Abnormalities were then subclassified into "A:" malformations which are true defects of morphogenesis, such as cyclopia; and "B": disruptions, dysplasias, deformations, and abnormalities which are secondary to abnormal morphogenesis and/or function of other important structures. An example of the latter is nystagmus, which in all cases is secondary, whether to a serious vision deficit, a neurologic abnormality, or albinism. Abnormalities, which can be present as either or both of the two subcategories, depending on the pathogenesis in a specific case, were marked as "A, B," for example a hoarse voice in a person with Williams' syndrome, which may be the result of abnormal morphogenesis of the larynx (A), but may also be the result of abnormal elastin in the vocal cords, in fact a dysplasia (B). As this classification list is developed for population

studies, we used the basic principle that the classification should be pathogenetically correct for the most prevalent appearance of the anomaly in the general Caucasian population.

Frequently, a finding in its usual presentation is a common variant, but the same finding in a more expressed form might be regarded a minor anomaly. For example, mild micrognathia is often seen in the general population, making micrognathia in general a common variant. However, if the mandible is extremely small but normally formed, it is a growth anomaly of phenogenesis, and, therefore, classified a minor anomaly, as in the Robin sequence. If it is small and malformed, as in the Hanhart anomaly, it is a malformation. Unfortunately, despite this clear distinction from a causal point of view, clinically it may be very difficult to discern. Similarly, an extreme presentation of a minor anomaly can sometimes be considered a malformation, for example microcephaly, defined as a head circumference below two standard deviations for age, in its most prevalent appearance is classified as minor anomaly, but in its extreme presentation, when secondary to decreased brain size, should be characterized as an abnormality. Hypoplasia of a structure is generally regarded a minor anomaly, but when extreme it should be scored as an aplasia, which is classified an abnormality.

Size-related findings were regarded as minor anomalies when size was below the 2nd centile (or <2 SD below the mean value) or above the 98th centile (or >2 SD above the mean value). For example, height above the 98th centile in its most prevalent appearance is scored a minor anomaly. However, when part of a general dysplasia, such as Marfan syndrome, it should be considered an abnormality. Of certain findings, like height below the 2nd centile, there is a presentation that is a minor anomaly, but the most prevalent presentation is as part of a syndrome, mainly hypochondroplasia. In this specific case, the general rule that a measurable item with a size below the 2nd centile should be tagged a minor anomaly does not hold: if the growth anomaly is part of a syndrome, it is always abnormal. For every size-related item, this principle was considered. For normal values of all listed anomalies, we refer to Hall et al. [1989].

Anomalies that are part of either a general or a very localized dysplasia, should all be classified as such, hamartomas being scored as dysplasias. However, when differentiating between a minor variant and an abnormality, the frequency of certain findings should also be taken into account. For example, a small nevus is a hamartoma and thus should in fact be classified a dysplasia, which is an abnormality. However, the prevalence is that high in the general population that this hamartoma can be classified as a common variant.

Isolated common variants will not alert physicians to search for an underlying developmental problem, and can thus be considered as less important. However, a combination of common variants may still point to a common defect. For example, the presence of isolated sparse hair in an otherwise normal individual should be regarded a common variant, but in combination with dystrophic nails it points to an ectodermal dysplasia. In general, it may be stated that the relative weight of a single minor anomaly is higher than that of a common variant. A combination of items in a single individual, however, either minor anomalies or common variants, may point to a more generalized defect such as a dysplasia, which may have larger implications for the individual.

Although the classifications in the present list apply to the Caucasian population, one should still realize that even within the Caucasian population differences exist. For example, brachycephaly is normal in persons of Turkish descent and most persons with other Eastern European background, but should be regarded a common variant in persons of North-Western European descent.

Furthermore, a finding may be scored differently in different age groups: facial hirsutism in an adult male is different from the same hirsutism in a child. Findings to which this principle applies are marked in the classification list (Table I) by an asterisk (*).

PATIENTS

In 1996, the Emma Children's Hospital, Academic Medical Center started an Outpatient Clinic for Late Effects of Childhood Cancer. All children with cancer who have completed the therapeutic regimen, and who were in remission for at least 5 years, are under regular control of the clinic. Patients are checked for possible symptoms, directed to the tumor itself, the side effects of the treatment, as on the psychosocial consequences of cancer in infancy and childhood, and its treatment.

All consecutive patients who visited the clinic were invited to participate in the study. Patients entered the study only after written permission was obtained from the patients themselves, or the parents in children and adolescents. The oncological case histories were extracted from the original medical records, and included the exact nature of the tumor and therapeutic regimens and family history. The family history pertaining to first- and second-degree relatives (extended if necessary) was also gathered directly from the patient and family (if present), with special attention for the presence of cancer, miscarriages, and congenital anomalies.

All newly diagnosed children with cancer were entered in this study prospectively; the work-up of the two groups was identical.

The primary investigator (JHMM) was a pediatrician, who was trained in the scoring of phenotypic findings by a pediatrician-clinical geneticist (RCMH).

The patients had a careful physical examination directed to abnormalities, minor anomalies, and common variants. It was a surface examination, so neither auscultation of the heart, nor abdominal palpation was performed. Any anomaly possibly caused by the tumor or the ensuing treatments, such as microcephaly following cranial irradiation or a leg length difference after abdominal irradiation, was not scored. If the examiner remained in doubt whether an anomaly was a result of therapy or not, the anomaly was not scored.

TABLE I. Classification List

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Build	Truncal obesity		X		2
	Generalized obesity		X		1
	Thin/slender build		X		2
	Muscular build	X			3
Stature	Short stature (proportionate)			A, B	11
	Short stature (short limbs)			A, B	5, 6
	Short stature (short trunk)			A, B	5, 6
	Tall stature (proportionate)		X		2
	Tall stature (long limbs)		X		2
Neurocranium: size	Microcephaly		X		2
	Macrocephaly		X		2
Neurocranium: shape	Brachycephaly		X		4, 12
	Dolichocephaly		X		4, 12
	Plagiocephaly	X			3, 12
	Trigonocephaly			A, B	5, 8, 9, 13
	Turricephaly			A, B	5, 8, 9, 13
	Kleeblattschedel			A	5, 13
Neurocranium: sutures	Ridged sutures		X		4
	Wide sutures		X		4
	Small anterior fontanel		X		2
	Early closure fontanels		X		4
	Delayed closure fontanels		X		4
	Extra fontanels			A	5
Hair: growth	Alopecia totalis			A, B	5, 6, 9
	Alopecia areata		X		4
	Sparse implantation	X			3
	Slow growth			B	6, 9
	Frontal balding/male pattern baldness	X*			3
	High anterior hairline	X			3
	Low anterior hairline	X			3
	Widow's peak		X		4
	Cow's lick	X			3
	Abnormal whorl (not-frontal)	X			3
Hair: structure	Fine	X			3
	Dry	X			3
	Soft	X			3
	Coarse	X			3
	Brittle		X		4
	Uncombable		X		4
	Kinky		X		4
Hair: pigmentation	Generalized hypopigmentation			A	5
	Patchy depigmentation			A	5
	Premature graying	X			3
	Unusual color		X		4
Face	Facial cleft			A	5
	Asymmetry		X		4
	Coarse face		X		4
	Small	X			3
	Narrow/elongated	X			3
	Broad	X			3
	Round-shaped	X			3
	Square-shaped	X			3
	Triangular-shaped		X		4
	Flat		X		4
	Lipodystrophy			A	5
	Premature aging			A	5
	Prominent creases		X*		4
	Expressionless/dull			B	9, 10
	Hypotonic			B	9, 10
	Hypoplastic malae		X		4
	Midface hypoplasia		X		4
	Midface hyperplasia		X		4
	Full cheeks	X			3
	Sunken cheeks	X*			3
	Broad lower 1/3 part		X		4
Nervus Facialis	Peripheral asymmetry			B	10
	Central asymmetry			B	10

(*Continued*)

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Forehead	Metopic ridge		X		4
	Frontal bossing		X		4
	Prominent		X		4
	Prominent glabella			A	5
	Glabella bone defect			A	5
	Sloping		X		4
	Ridged	X*			3
	Broad/wide	X			3
	Short		X		4
	Biparietal narrowing		X		4
	Hyperplastic supra-orbital ridges	X			3
	Hypoplastic supra-orbital ridges		X		4
Eyes: general	Cyclopia			A	5
	Asymmetry		X		4
	Strabismus	X			3
	Nystagmus			B	9, 1
	Duane (retraction) anomaly			B	9
	Deeply-set		X*		4
	Proptosis		X		4
	Microphthalmos			A	5
	Buphthalmos			A	5
	Cryptophthalmos			A	5
	Orbital cysts			A	5
Eyes: iris	Aniridia			A	5
	Hypoplasia			A	5
	Atrophy/dysplasia			A, B	5, 6
	Coloboma (uni-/bilaterally)			A	5
	Brushfield spots	X			3
	Heterochromia			A	5
	Hypopigmentation			A	5
	Iris stellata	X			3
Eyes: pupils	Ectopic pupils			A	5
	Abnormal size or movement			B	9, 10
	Asymmetry		X		4
	Persistent pupillary membrane			A	5
Eyes: lens	Ectopia lentis			A	5
	Size/shape abnormality			A	5
	Cataract			A, B	5, 6, 9
Eyes: cornea	Microcornea		X		2
	Macrocornea		X		2
	Cloudy cornea			A, B	5, 6, 9
	Anesthesia			B	10
Eyes: conjunctivae	Noduli	X			3
	Teleangiectasia		X		4
	Epibulbar dermoids			A	5
Eyes: sclerae	Blue colored			B	6
	Naevus of ota			A	5
Eyes: eyelids	Ptosis		X		4
	Coloboma upper-/lower lid			A	5
	Ectropion		X		4
	Entropion		X		4
	Synechiae/ankyloblepharon			A	5
	Edema		X		4
	Fullness	X			3
	Full lateral parts	X			3
Palpebral fissures	Blepharophimosis		X		2
	Short		X		2
	Wide		X		2
	Asymmetry		X		4
	Mongoloid slant		X		2
	Antimongoloid slant		X		2
	Almond-shaped	X			3
	Bow-shaped		X		4
Peri-orbital skin	Epicanthi		X		4
	Telecanthi		X		4
	Blepharochalasis		X		4
	Skin tag			A	5
	Infra-orbital skin folds		X		4

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Intercanthal distance	Hypotelorism		X		2
	Hypertelorism		X		2
Eyelashes	Absent			A	5
	Sparsely implanted	X			3
	Prominent	X			3
	Double			A	5
	Coloboma			A	5
	Two-colored		X		4
Eyebrows	Absent			A	5
	Hypoplasia	X			3
	Sparse	X			3
	Double			A	5
	Synophrys	X			3
	Medial flare	X			3
	Lateral flare	X			3
	Medial & lateral flare	X			3
	Narrow laterally	X			3
	Arched	X			3
	Continuing far laterally	X			3
Lacrimal glands	Decreased tear production			A, B	5, 6, 9
Nasolacrimal ducts	Absent			A	5
	Extra			A	5
	Abnormal position			A	5
Nose: general	Absent			A	5
	Choanal atresia/stenosis			A	5
	Cleft			A	5
	Large	X*			3
	Flat		X*		2
	Small/short		X		2
	Long		X		2
	Broad	X			3
	Pinched		X		4
	Low hanging columella	X			3
	Profile convex	X			3
	Profile concave	X			3
	Nasal tip deviated		X		4
	Septum deviation		X		4
	Hairy polyp			B	6
Nose: alae	Hypoplasia	X			3
	Coloboma			A	5
Nose: nares	Broad	X			3
	Single			A	5
	Flare	X			3
	Anteversion		X		4
	Asymmetry		X		4
	Supernumerary			A	5
Nose: bridge	Flat		X*		4
	Prominent/high	X			3
	Wide	X			3
Nose: tip	Bifid		X		4
	Broad	X			3
	Flat		X		4
	Bulbous	X			3
	Overhanging		X		4
Nose: septum	Absent cartilage			A	5
	Short		X		4
	Broad		X		4
	Narrow		X		4
Nose: base	Broad	X			3
	Narrow	X			3
Upper jaw	Cleft			A	5
	Hypoplastic		X		4
	Prominent		X		4
	Narrow	X			3
	Asymmetry		X		4
	Absent premaxilla			A	5
	Prominent premaxilla		X		4

(*Continued*)

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Lower jaw	Absent			A	5
	Cleft			A	5
	Asymmetry		X		4
	Prominent	X			3
	Retro-/micrognathia	X			3
Chin	Dimpled/grooved	X			3
	Pointed		X		4
Voice	Aphonia			A, B	5, 9, 10
	Nasal			B	9, 10
	Dysarthria			B	9, 10
	Hoarse			A, B	5, 6, 9, 10
	Cat's cry/high-pitched			B	6, 9, 10
	Low-pitched			B	6, 9, 10
Philtrum	Long		X		2
	Short		X		2
	Smooth	X			3
	Prominent/deep	X			3
Oral region	Extra oral frenulae			A	5
	Oral synechiae			A	5
	Prominent nasolabial folds	X*			3
	Oral pigmentation		X		4
	Peri-oral pigmentation		X		4
Mouth	Microstomia		X		2
	Macrostomia		X		2
	Asymmetry		X		4
	Open mouth appearance			B	9, 10
	Pouting		X		4
	Upturned corners		X		4
	Downturned corners		X		4
Upper lip	Cleft (midline vs. non-midline)			A	5
	Thin	X			3
	Full/thick	X			3
	Tight		X		4
	Everted		X		4
	Pit(s)			A	5
	Cupid bow		X		4
Lower lip	Cleft			A	5
	Pit(s)			A	5
	Full/thick	X			3
	Thin	X			3
	Tight		X		4
	Everted/drooping		X		4
Alveolar ridges	Fusion gums and/or jaw			A	5
	Hypertrophy			A, B	5, 6, 9
Palate	Cleft			A	5
	High/narrow		X		2
	Short		X		2
	Wide		X		2
	Fistulae			A	5
	Cleft uvula			A	5
	Absent			A	5
	Hypoplastic uvula		X		4
	Long uvula		X		4
	Prominent lateral ridges/rugae		X		4
Alveolar ridges	Thick/wide		X		4
	Cleft			A	5
Tongue	Aplasia			A	5
	Hypoplasia		X		4
	Cleft			A	5
	Large		X		4
	Lobulated			A	5
	Smooth		X		4
	Prominent groove(s)			A, B	5, 6, 9
	Ankyloglossia		X		4
	Glossoptosis			A, B	5, 10
	Protruding tongue			B	10
	Fasciculations			B	10

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Teeth	Macrodontia		X		2
	Microdontia		X		2
	Supernumerary teeth			A	5
	Oligodontia			A	5
	Single central incisor			A	5
	Advanced eruption		X		2
	Delayed eruption		X		2
	Neonatal teeth			A	5
	Premature loss teeth			A, B	5, 6, 9
	Dental crowding	X			3
	Malocclusion	X			3
	Widely spaced	X			1
	Abnormally shaped teeth			A	5
	Asymmetry		X		4
	Fusion incisors			A	5
	Diastema	X			3
	Dentin anomalies			B	6
	Enamel anomalies			B	6
Ears: general	Agenesis			A	5
	Small		X		2
	Aplasia/microtia			A	5
	Large		X		2
	Asymmetry		X		4
	Long ears		X		2
	Flat ears	X			3
	Increased A–P diameter (=round)		X		2
	Decreased A–P diameter (=narrow)		X		2
	Dysplastic ears		X		4
	Simple ear		X		4
	Cupshaped			A	5, 10
	Lop ear			A	5
	Crumpled			B	6, 8
	Low-set		X		2
	Posteriorly rotated		X		2
	Prominent	X			1
	Cystic pinna			A, B	6, 8, 9
	Calcification cartilage		X		4
Ears: helices	Hypoplastic/thin	X			3
	Abnormally modeled		X		4
	Overfolded	X			3
	No fold	X			3
	Notched	X			3
	Horizontal upper ridge	X			3
	Darwin “Lump”	X			3
	Pit(s)			A	5
Ears: lobules	Absent/hypoplastic	X			3
	Large/hyperplastic	X			3
	Attached	X			3
	Uplift	X			3
	Crease		X		4
	Cleft			A	5
Ears: tragus	Absent			A	5
	Hypoplastic		X		4
Ears: meatus	Absent			A	5
	Atresia			A	5
	Narrow		X		4
Ears: pits	Unilateral			A	5
	Bilateral			A	5
Ears: tags	Unilateral			A	5
	Bilateral			A	5
Neck	Branchial cyst/cleft/sinus			A	5
	Webbing			A, B	5, 9
	Cystic hygroma			A, B	5, 9
	Long	X			3
	Short	X			3
	Thick/broad	X			3
	Torticollis			B	9, 10

(*Continued*)

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
	Loose skinfolds		X		4
	Goiter			A, B	5, 9
Thorax	Broad		X		2
	Narrow		X		2
	Increased A–P diameter		X		2
	Asymmetry		X		4
	Short		X		4
	Long		X		4
	Flat	X			3
	Flaring		X		4
	Xiphisternum			A	5
	Pectus Carinatum		X		4
	Pectus Excavatum		X		4
	Short sternum		X		2
	Sternum asymmetry		X		4
Mammae	Absent			A	5
	Hypoplasia		X		4
	Hypertrophy	X			3
	Asymmetry		X		4
	Gynecomastia			A, B	5, 9
	Pseudo-gynecomastia		X		4
	Premature development	X			16
Nipples	Absent			A	5
	Hypoplastic		X		4
	Large/hyperplastic		X		4
	Asymmetry		X		4
	Supernumerary			A	5
	Wide-spaced		X		2
	Inverted	X			3
Shoulders	Broad	X			3
	Narrow	X			3
	Sloping	X			3
	Anteriorly rotated			B	9
Clavicles	Absent			A	5
	Hypoplastic		X		4
	Long		X		4
	Horizontal	X			3
Scapulae	Absent			A	5
	Small		X		4
	High/sprengel			A	5
	Winged		X		4
M. pectoralis	Absent			A	5
	Hypoplasia		X		4
Ribs	Absent			A	5
	Prominent bows		X		4
Abdomen	Diastasis recti		X*		4
	Muscle aplasia			A	5
	Muscle hypoplasia		X		4
	Protruberant	X			3
	Gastroschisis			A	5
	Abnormal umbilicus position		X		4
	Hernia umbilicalis			B	6, 9
	Omphalocele			A, B	5, 9
	Hernia inguinalis			B	6, 9
Anus	Atresia			A	5
	Stenosis			A, B	5, 9
	Abnormal position		X		4
	Fistula			A, B	5, 7
Genitalia: general	Ambiguous			A	5
	Pubertas praecox	X			16
	Pubertas tarda	X			16
Genitalia: female	Prominent clitoris		X		4
	Prominent labia majora		X		4
	Prominent labia minora		X		4
	Hypoplasia labia majora		X		4
	Hypoplasia labia minora		X		4
	Fusion labia			A	5

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
	Vaginal atresia			A	5
	Vaginal hypoplasia		X		4
	Vaginal septum			A	5
	Rectovaginal fistels			A, B	5, 7, 9
	Cloaca			A	5
Genitalia: male	Small penis		X		2
	Large penis		X		2
	Burried penis	X			3
	Hypoplasia preputium		X		4
	Hypospadia			A	5
	Epispadia			A	5
	Large testes		X		2
	Small testes		X		2
	Cryptorchid testes			A	5
	Hydrocele testis		X		4
	Supernumerary testes			A	5
	Hypoplasia scrotum		X		4
	Overriding/shawl scrotum	X			3
	Bifid scrotum			A	5
Back	Decreased lumbar lordosis	X			3
	Decreased thoracic kyphosis/straight back		X		4
	Increased lumbar lordosis	X			3
	Increased thoracic kyphosis		X*		4
	Scoliosis			A, B	5, 6, 8, 9, 10
	Rigid spine			A, B	5, 6
	Buffalo hump		X		4
Spinal cord	Spina bifida			A	5
	Meningocele/myelomeningocele			A	5
	Syringomyelia			A	5
	Pilonidal cyst		X		4
	Tethered cord			A, B	5, 6
Sacrum	Sacral dimple/sinus	X			3
	Caudal appendage			A	5
	Asymmetric crease		X		4
	Fat pads		X		4
Upper limbs	Absent			A	5
	Proportionally short arms		X		2
	Rhizomelia			A	5
	Mesomelia			A	5
	Acromelia			A	5
	Overgrowth		X		4
	Hemihypertrophy		X		4
	Reduction deformity/deficiency (some digits)			A, B	5, 7
	Reduction deformity/deficiency (no digits)			A, B	5, 7
	Constriction rings			B	7
	Asymmetry		X		4
Humerus	Absent			A	5
	Bowed			A, B	5, 6, 8
Elbows	Valgus	X			3
	Webbing			B	9
	Acromial dimple			B	8
Forearm	Absent			A	5
	Bowed			A, B	5, 6, 8
	Madelung deformity			A	5
Hands	Absent			A, B	5, 7
	Malproportionate small		X		2
	Malproportionate large		X		2
	Narrow		X		2
	Broad		X		2
	Asymmetry		X		4
	Ectrodactyly			A	5
	Syndactyly		X		4
	Trident hand		X		4
	Clubhands			A, B	5, 8, 9, 10

(*Continued*)

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
	Clenched			B	10
	Ulnar/radial deviation			B	5, 8, 9, 10
	Long handpalm		X		2
	Thenar hypoplasia		X		4
	Hypothenar hypoplasia		X		4
	Edema dorsum hands		X*		4
	Isolated metacarpal shortening		X		2
Palmar creases	Sydney crease		X		4
	Simian crease		X		4
	Bridging crease		X		4
	Absent			B	9, 10
	Decreased flexion creases		X		4
	Deep creases		X		4
Fingers	Absent/oligodactyly			A, B	5, 7
	Hypoplastic		X		2
	Polydactyly (pre-axial)			A	5
	Polydactyly (post-axial)			A	5
	Polydactyly (meso-axial)			A	5
	Mirror image polydactyly			A	5
	Long fingers		X		2
	Arachnodactyly			B	6
	Short fingers		X		2
	Brachydactyly (Bell's types)			A, B	5, 6
	Macrodactyly		X		2
	Broad fingers	X			3
	Camptodactyly		X		4
	Clinodactyly	X			3
	Ulnar deviation dig II–III	X			3
	Ulnar deviation dig V		X		4
	Radial deviation dig IV–V	X			3
	Overlapping			B	8, 9, 10
	Symphalangism			A	5
	Syndactyly		X		4
	Tapering		X		4
	Clubbing			B	9
	Wide fingertips		X		4
	Fetal pads	X			3
	Short endophalanges		X		4
	Absent phalanges			A, B	5, 7
	Constriction rings			B	7
Thumbs	Absent			A, B	5, 7
	Hypoplasia		X		4
	Asymmetry		X		4
	Broad		X		4
	Adducted			B	9, 10
	Proximal placement		X		4
	Hitch-Hiker's thumb			B	6
	Triphalangeal			A	5
	Short endphalanges		X		4
Pelvis	Broad		X		2
	Narrow		X		2
	Hip dislocation			A, B	5, 6, 9, 10
Lower limbs	Absent			A, B	5, 7
	Proportionally short legs		X		2
	Rhizomelia			A	5
	Mesomelia			A	5
	Acromelia			A	5
	Sirenomelia			A	5
	Duplication			A	5
	Asymmetry		X		4
	Overgrowth		X		4
	Hemihypertrophy		X		4
	Reduction deformity/deficiency (no digits)			A, B	5, 7
	Reduction deformity/deficiency (some digits)			A, B	5, 7
	Constriction rings			B	7

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Femur	Absent			A	5
	Bowed			A, B	5, 6, 8
Patella	Absent			A	5
	Hypoplastic		X		4
Knee	Varum		X*		4
	Valgum		X*		4
	Webbing			B	9, 10
Tibia	Absent			A	5
	Bowed			A, B	5, 6, 8
Feet	Absent			A, B	5, 7
	Malproportionately small		X		2
	Malproportionately large		X		2
	Short		X		2
	Long		X		2
	Narrow		X		2
	Broad		X		2
	Asymmetry		X		4
	Pes planus	X			3
	Pes cavus	X			3
	Talipes equinovarus			A, B	5, 10
	Ectrodactyly			A	5
	Prominent heel		X		4
	Rockerbottom			A	5
	Deep plantar creases		X		4
	Fetal pads	X			3
	Edema dorsum feet		X*		4
	Isolated metacarpal shortening		X		4
Toes	Absent			A, B	5, 7
	Hypoplastic		X		4
	Pre-axial polydactyly			A	5
	Meso-axial polydactyly			A	5
	Post-axial polydactyly			A	5
	Mirror-image polydactyly			A	5
	Long		X		4
	Short		X		4
	Broad	X			3
	Short terminal phalanges		X		4
	Syndactyly II–III			A	5
	Partial syndactyly II–III		X		4, 14
	Syndactyly (not II–III)			A	5
	Partial syndactyly (not II–III)		X		4, 14
	Symphalangism			A	5
	Widely spaced	X			3
	Sandal gap	X			3
	Overriding	X			3
	Clinodactyly dig V	X			3
	Hammertoes		X		4
	2nd toe longer than 1st	X			1
	Fetal pads	X			3
Halluces	Absent			A, B	5, 7
	Hypoplasia		X		4
	Short		X		4
	Long		X		4
	Asymmetry		X		4
	Broad		X		4
	Narrow		X		4
	Varus		X*		4
	Valgus		X*		4
	Proximal implantation	X			3
	Dorsiflexed/hammertoe		X		4
Joints	Contracture			A, B	5, 8, 9, 10
	Contractures (incl. arthrogryposis)			A, B	5, 6, 8, 9, 10
	Dislocation			A, B	5, 8, 9, 10
	Dislocations			B	6, 8, 9, 10
	Enlargement		X		4
	Hypomobility small joints		X		4

(*Continued*)

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
	Hypomobility large joints		X		4
	Hypomobility small and large joints			B	6, 8, 9, 10
	Hypermobility small joints		X		4
	Hypermobility large joints		X		4
	Hypermobility small and large joints			B	6, 8, 9, 10
Muscles	Isolated agenesis			A	5
	Hypoplasia		X		4
	Atrophy/dystrophy			B	6, 9, 10
	Hypertrophy			A, B	5, 9, 10
	Hypotonia			B	10
	Hypertonia			B	10
	Muscle weakness			A, B	5, 10
	Fasciculation			B	10
	Myotonia			A, B	5, 10
Neurology	Hemiplegia/paresis			B	10
	Diplegia/paresis			B	10
	Tetraplegia/paresis			B	10
	Spasticity			A, B	5, 7, 10
	Cranial nerve palsy			A, B	5, 7, 10
	Tremor			B	10
	Developmental delay			A, B	5, 6, 7, 8, 9, 10
Skin: general	Atrophy			A, B	5, 6, 8, 9
	Thin, translucent skin		X		4
	Thick		X		4
	Hyperkeratosis		X		4
	Ichtyosis			B	6
	Dry skin	X			3
	Cutis laxa			B	6
	Hyperelasticity		X		4
	Excessive skin folds			A, B	5, 6, 8
	Slow healing			B	6, 9
	Abnormal scarring			B	6, 9
	Photosensitivity			B	6, 9
	Lipodystrophy			A, B	5, 6
	Cutis marmorata	X			3
	Poikiloderma	X			3
	Lymphedema			A, B	5, 6, 9
	Calcification			B	6, 9
	Dimples		X		4
Skin: localized	Hypoplasia/aplasia			A, B	5, 6, 8, 9
	Atrophy			A, B	5, 6
	Striae	X*			3
	Bullae			A, B	5, 6, 9
	Scleroderma			B	6
	Fibromata	X			3
	Lipomata			B	6
	Xanthomata			B*	6, 16
	Scalp defects			A, B	5, 6, 7
Skin: pigmentation	Albinism			A	5
	Generalized hypopigmentation		X		4
	Generalized hyperpigmentation		X		4
	Hypo-/depigmentation patches		X		4
	Hyperpigmentation patches		X		4
	Cafe au lait (solitary)	X			3
	Cafe au lait (multiple)			A	5
	Solitary naevus (size >0.5 cm)	X			1
	Multiple naevi (size >0.5 cm)		X		2
	Linear sebaceus naevus			A	5
	Axillary freckling		X		4
	Acanthosis nigricans			A, B	5, 6
Skin: vascular	Capillary hemangioma			A	5
	Hemangioma plana			A	5
	AV malformation			A	5
	Stork bite	X			3
	Angel's kiss	X			3
	Multiple telangiectiasia			A, B	5, 6, 9
	Prominent vessels	X			3
	Multiple haematoma			B	6, 9

TABLE I. (*Continued*)

Structure	Trait	Common variant	Minor anomaly	Abnormality	Comment
Skin: body hair	Generalized	X*			3
	Localized	X*			3
Nails	Absent			A, B	5, 7
	Hypoplasia		X		4
	Short		X		4
	Narrow		X		4
	Concave		X		4
	Hyperconvex		X		4
	Thin/brittle		X		4
	Thickened		X*		4
	Pits	X			3
	Striped	X			3
	Bifid/double			A	5
	Fused			A	5
	Abnormal color		X		4

*Dependent on age.
A = malformation; B = deformation, disruption, dysplasia, or other abnormality secondary to abnormal morphogenesis or function of other structures.
The numbers given under the column head Comments connote:
1. Anomaly resulting from a defect in phenogenesis, is measurable, shows a Gaussian distribution. The most prevalent appearance has a frequency of more than 4%.
2. Anomaly resulting from a defect in phenogenesis, is measurable, shows a Gaussian distribution. The most prevalent appearance has a frequency of 4% or less.
3. Anomaly resulting from of a defect in phenogenesis, either is measurable but normal values are lacking or is not measurable. The most prevalent appearance has a frequency more than 4%.
4. Anomaly resulting from of a defect in phenogenesis, either is measurable but normal values are lacking or is not measurable. The most prevalent appearance has a frequency of 4% or less.
5. Malformation secondary to a defect in the embryogenesis.
6. Dysplasia.
7. Disruption.
8. Deformation.
9. Abnormality secondary to dysfunction of other structures/other disorders.
10. Abnormality secondary to neurologic dysfunction.
11. Although height is a measurable feature with a Gaussian distribution, height below P3 is not scored as a minor anomaly, as the most prevalent presentation is as a dysplasia or malformation syndrome.
12. The most prevalent appearance is a variation of normal not caused by a craniosynostosis.
13. Always the result of a craniosynostosis.
14. Defined as 1/3 or more from the base of the toe.
15. Should only be scored in children, as it is very common in adults.
16. The most prevalent presentation is as a variation of normal physiology with a frequency of more than 4%.

The scoring of findings was on a single sheet indicating only the general body parts. To prevent overscoring, the findings were not listed separately. All patients were scored by a single investigator (JHMM). A second investigator (RCMH) scored 10% of all patients over the course of the study, to allow determination of interobserver variation. If the first investigator remained in doubt as to the presence of an anomaly, photographs were taken and discussed with the second investigator.

All data were entered in the "Amsterdam Dysmorphology Database," an SPSS database (SPSS Data Entry 3.0) designed specifically for entry and analysis of data regarding phenotype, clinical history, family history, and results of additional investigations. All anomalies can be scored under 98 subheadings or items, based on our classification list.

RESULTS

Classification List

Table I shows the list classifying the collected series of abnormal morphological findings. The 29 major anatomical or functional areas (not shown in the list) are subdivided into 98 smaller areas which are finally divided into a total of 683 single anomalies, each categorized as a common variant, minor anomaly, or abnormality.

Every one of the 683 findings was first considered in a similar manner by three investigators (JHMM, CDMvK, and RCMH) independently. Every item on which either of us disagreed was discussed until consensus was reached based on the same basic principles.

Again it should be mentioned that as this list was developed for population studies, we used the basic principle that the classification should be correct for the most prevalent appearance of the finding in the general Caucasian population. An example demonstrating the application of this principle is the item "neurocranium (shape)" which encompasses (1) brachy-, (2) plagio-, (3) dolicho-, (4) trigono-, and (5) turri-cephaly. Brachy- and plagio-cephaly are considered common variants based on their expected prevalence in the normal population of >4%. However, dolichocephaly is regarded a minor anomaly as it is seldomly seen. Neither brachy- nor plagio- or dolicho-cephaly are considered abnormalities since in their most prevalent appearance they result from abnormal phenogenesis or developmental fine-tuning. However, trigonocephaly and turricephaly are

always the result of pathology, i.e., craniosynostosis, and should, therefore, be regarded abnormalities.

Pilot Application

During a 3-month period, 102 consecutive former patients were seen at the late effects clinic, of whom only two refused participation in our study. The reason for refusal in both cases was an actual psychological revival of the period during which they had been intensely treated, which made them afraid of all hospital related matters. In fact, both patients totally refused any further follow up at the late effects clinic. The medical records of both former patients were checked for possible congenital anomalies or syndromes, which could have made them ashamed of their physical appearance and thereby could have introduced a selection bias, but no anomaly or syndrome was found. Of the remaining 100 persons, 95 were white Caucasians, 1 was from Northern Africa, and 4 had a mixed racial background. Mean age of the population was 25 years, 53 were males and 47 females. Forty-four were treated for leukemia or lymphoma and 56 for a solid tumor.

Although our aim was to determine the interobserver variation in 10%, in the first 100 persons, we determined possible variation in 31. In total, 3,038 items were scored (Fig. 2), 126 items were tagged positive and 2,885 negative by both examiners. The examiners disagreed on 27 items: observer A regarded 18 items positive, where observer B did not, observer B scored 9 items positive, where observer A did not. So in 31 of the first 100 persons, the interobserver variation was determined, yielding a kappa score of 0.89.

DISCUSSION

We created a list of all physical anomalies detectable by surface examination, based on a generally accepted nomenclature [Winter and Baraitser, 2001] and uniform classification system [Aase, 1990b]. The list will enhance uniformity in the scoring and classification of physical abnormalities, allowing investigators to generate normal values and to evaluate systematically the presence of patterns in phenotypic anomalies, both in the general population as well as in patient populations with various disorders. The classification system is based on two criteria: the (suspected) pathogenesis of a finding and the prevalence in the normal population. This will allow weighing the importance of the scored items in the population under study, and will facilitate assessment of possible developmental problems in a large variety of study populations with a suspected developmental pathogenesis. Furthermore, it may allow discriminating different subgroups of patients in heterogeneous patient populations, subgroups, which may have their own specific pathogenesis, treatment, and prognosis. Numerous investigators have reported an apparently increased incidence of congenital anomalies in a variety of disorders. However, almost all are hampered by their inability to consider the biologic relevance of the individual items scored [Frías and Carey, 1996]. In their review on "mild errors of morphogenesis (MEM)" Frías and Carey strongly encourage future studies to consider the biologic relevance of each recorded MEM and give it an appropriate weight [Frías and Carey, 1996]. Therefore, we started our study by creating this list of all physical anomalies detectable by surface examination. We realize that creating a uniform classification system will induce generalizations. Although this might be a drawback for the study of an individual patient, a uniform system is an advantage and considered even a conditio sine qua non when studying populations as it is the only way to consider the biologic relevance of the items scored. One might argue that the creation of a list based on the pathogenesis of all anomalies is impossible, as the exact pathogenesis of many findings still remains to be elucidated. However, for a large number of anomalies the pathogenesis is known and for many others there are strong indications of a suspected pathogenesis, allowing the creation of a classification based on current knowledge. However, it will be a dynamic list that will be adjusted as new theories on pathogenesis develop.

		Examiner B	
		normal	abnormal
Examiner A	normal	2885	9
	abnormal	18	126

Fig. 2. Cross-table summarizing the number of items scored normal and abnormal by two observers in 31 patients.

Although the definitions of all items in our list are based on the nomenclature as used in the LDDB, it should be realized that the definitions as given by Winter and Baraitser [2001] still leave room for interpretation of the individual anomalies. We agree with Frías and Carey [1996] that standardization of the current nomenclature of all individual items by a group of international experts would greatly improve and facilitate future studies on the epidemiologic behavior of both abnormalities and minor variants.

The list was created to study several populations of interest at our institution, all with a suspected developmental etiology: children with cancer, with mental retardation, and with autism. To determine the feasibility of the list in a patient group, a pilot study on patients who had cancer as a child is shown in this paper. In a 3-month period, we performed a surface examination directed at morphological anomalies in 100 former cancer patients. Using our list, the interobserver variation was determined in 31 patients leading to an excellent agreement. This also shows that morphological anomalies can be screened accurately also by nonclinical geneticists if trained in clinical morphology, as was shown earlier in two studies [Hook, 1971; Méhes, 1988]. Hook [1971] reported less than 1%, and Holmes [1982] less than 2% disagreement between two nonclinical geneticists in the identification of surface morphological anomalies. However, in a later study, Holmes et al. [1987] found markedly greater interobserver differences in the detection of subjective and even in objective anomalies. During a 2-year period, 444

infants were examined separately by two examiners—a physician and a non-physician—looking for the prevalence of 114 "minor physical features." The kappa analysis showed an excellent agreement for six findings (kappa 1.0–0.75); the agreement was good for 33 (kappa 0.75–0.5), but poor for the remaining 77 anomalies (kappa <0.5). Although the prevalence of objective anomalies in the first group (kappa 1.0–0.75) will have been higher, it is hard to understand the large difference in scoring of relatively objective anomalies such as Sydney creases and epicanthal folds (kappa 0.33 and 0.28). Taking a close look at their table, it seems that one of the two examiners consistently had a higher score throughout the different types of anomalies. The reason for this discrepancy remains unclear as the training in clinical morphology of the non-physician is not discussed in the article [Leppig et al., 1987].

Until now, seven earlier studies were performed describing the prevalence of minor physical anomalies in pediatric cancer patients [Kobayashi et al., 1968; Stojimirovic, 1981; Méhes et al., 1985, 1994, 1998; Fekete et al., 1987; Roganovic et al., 2002]. Méhes et al. [1985] was able to examine 106 pediatric cancer patients. An equal number of age-matched controls with acute infectious diseases and 81 healthy sibs of 62 index patients were examined in a similar way. Anthropometric indices of patients did not differ from those of the controls. The frequency of "major congenital anomalies" was about equal in all three groups. However, minor anomalies were significantly more prevalent in the pediatric cancer patients and their sibs compared to controls: 69.2% of patients, 63.0% of sibs, and 34.6% of the control subjects had at least one apparent minor anomaly. This shows the advantage of the study of minor anomalies: their prevalence is much higher than the prevalence of major anomalies and specific patterns of anomalies are more easily detected. In the first Méhes study, the total group of patients was composed of 18 different malignancy groups, preventing the detection of specific associations of anomalies or patterns of anomalies. In a later study, Méhes specifically focused on 54 acute lymphoblastic leukemia (ALL) patients and their families [Méhes et al., 1994], confirming the increased prevalence of minor anomalies in ALL patients and their sibs. The study was extended and reported in 1998 [Méhes et al., 1998]: 100 leukemia patients, the majority of their parents, and sibs were examined. In 40% of the subjects, the interobserver variation was determined revealing a concordance rate of 79%, which is reliable. Again, a significantly higher prevalence of anomalies was found in ALL-patients and their sibs, compared to parents and controls. When age-dependent anomalies were removed, the difference remained significant. However, when both age-dependent and familial anomalies were excluded from the analysis, the statistical difference disappeared. No specific association of ALL with a particular anomaly was found. Méhes concluded that an increased prevalence of anomalies in sibs of children with ALL "cannot be regarded as a sign of predisposition for leukemia. One can only speculate on a possible recessive association of MEM's with ALL, on possible maternal inheritance, or on developmental genes that may be involved in the processes of malignancy and disturbed morphogenesis as well" [Méhes et al., 1998]. Arguing along this line, familial occurring anomalies should not be excluded from analysis, while studying a specific patient group: familial anomalies should be regarded as valuable as their non-familial occurring counterparts, as they might point to patterns induced by aberrant developmental genes, with a low penetrance for cancer in childhood.

An early Japanese study seems to confirm the findings of the Swiss group, the major drawback of the study being that patients were not examined personally by the investigators [Kobayashi et al., 1968]. From 1966 to 1968, 371 cases of childhood malignancy were registered at the Childhood Cancer Registry of the Tokyo Metropolitan Area. A table of major and minor congenital anomalies was sent to the hospitals and data were provided by each of the pediatricians in charge. It is not clear from the paper whether the patients were especially examined by the pediatricians with specific attention for congenital anomalies. A control group of 123 cases without malignancies or congenital malformations was examined on major and minor anomalies while they were visiting the outpatient clinic of the University of Tokyo Hospital. The incidence of anomalies in children with a malignancy was 41%, 20% having a major and 32% having a minor anomaly. In the control group, the incidence of anomalies (major and/or minor grouped together) was 13% ($P < 0.001$). Numbers were too small to allow any correlation between specific childhood tumors and individual or patterns of anomalies. The higher incidence of minor anomalies in the Swiss group may be explained by three factors: since the list of minor anomalies was not published in the Japanese study, they might have checked for less traits than the 57 traits used by the Swiss group. Furthermore, in the Japanese study the patients may not be specifically examined by the pediatrician focused on congenital anomalies, which also might underscore the existence of minor anomalies. And, finally, the pediatricians may have been less trained compared to the Swiss investigators to score for minor anomalies.

Fekete et al. [1987] studied 55 minor anomalies in 51 children with leukemia, and 49 with different solid tumors. The prevalence in the patient-group (85%) was significantly higher than in a group of 100 healthy controls (66%). Two or more anomalies were found in 58% of the patients, versus 23% in controls, a significant difference. No significant tumor specific association of a given pattern of anomalies could be demonstrated.

Only recently, a 7th study was undertaken describing the frequency and type of anomalies in 64 children with hematological malignancies treated between 1983 and 1997 [Roganovic et al., 2002]. Eighty-six percent had at least one minor anomaly compared to 67% in 64 age and gender matched controls. Unfortunately, a different list was used and definitions of what to consider a minor anomaly were not given. From the seven studies one can conclude: (1) patients with malignancies appear to have more congenital anomalies than control children, suggesting the existence of prenatal factors causing both anomalies and cancer, (2) each time the numbers were

too small to determine any significant correlation between tumor types and (combinations of) individual anomalies, and (3) the studies did not provide definitions of each minor or major anomaly, and subsequently using different lists of anomalies were used making comparison very difficult.

In the past three decades, numerous studies reported the incidence of minor physical anomalies in a variety of disorders: diabetes [Méhes et al., 1986], metabolic diseases [Méhes, 1991], isolated urinary tract malformations [Méhes and Pinter, 1990], mental retardation [Smith and Bostian, 1964; Firestone et al., 1978; Meggyessy et al., 1980; Van Karnebeek et al., 2002a], cerebral palsy [Miller, 1989; Coorssen et al., 1991], hyperactivity [Waldrop and Goering, 1971; Quinn and Rapoport, 1974; Firestone et al., 1978], autism [Links et al., 1980; Accardo et al., 1991; Miles and Hillman, 2000; Van Karnebeek et al., 2002b], and schizophrenia and mood disorders [Gualtieri et al., 1982; Guy et al., 1983; Green et al., 1989, 1994a,b; Lohr and Flynn, 1993; Alexander et al., 1994; O'Callaghan et al., 1995; Lane et al., 1997; Trixler et al., 1997; Griffiths et al., 1998; Ismail et al., 1998, 2000; Lawrie et al., 2001; Trixler et al., 2001; Scutt et al., 2001; McGrath et al., 2002]. A few studies deserve more attention here. Miles and Hillman [2000] did an exemplary study on minor physical anomalies in 133 autistic individuals, most of their parents, and a substantial number of grandparents and sibs. Each physical finding was standardized according to the LDDB [Winter and Baraitser, 2001], and divided into three groups: (1) minor anomalies, "structural anomalies that occur in $<5\%$ of the population," (2) measurement abnormalities that are beyond 2 SD from the mean, (3) descriptive traits (often called spectrum variants), with a prevalence of $>4\%$, which are often familial and cannot be accurately measured, and (4) malformations. This classification system closely resembles our list, although in our system minor anomalies and measurement anomalies are grouped in one category and collectively called minor anomalies. Descriptive traits or spectrum variants resemble our common variants. Nothing is stated about dysplasias, disruptions, or deformations. Using this classification system, the subjects were categorized from "normal," to "minimal," "mild," "moderate," and "severe," or to "syndrome," thus weighing the severity of the findings in all individuals. Individuals categorized from moderate to severe were called "phenotypically abnormal." In this subgroup (20% of the total group), five established syndromes were diagnosed compared to one in the remaining 80%, suggesting that this subgroup has a different cause from the phenotypically normal to intermediate group of autistic individuals. In his editorial comment, Opitz [2000] complimented the authors on using the method of analysis of family resemblance, and indeed family resemblance is of great importance in the individual patient. However, as stated earlier, familial occurring minor anomalies, categorized as "descriptive traits" in the study by Miles and Hillman [2000], might point to patterns induced by aberrant developmental genes, with a low penetrance for the specific disorder, and thus might be of great importance when studying groups of patients with that disorder. Therefore, in our classification system, designed for population studies, anomalies that arise during phenogenesis with a prevalence of $\leq 4\%$ will be classified minor anomalies, regardless of familial occurrence. Sorting phenogenetic anomalies into different categories defined by their prevalence in the general population might seem artificial in the individual patient as they basically refer to the same phenomenon of abnormal phenogenesis [Opitz, 2000]. However, a very low prevalence of an anomaly in the general population indicates that its presence in an individual is exceptional and should be regarded as more important than the presence of a more commonly occurring anomaly of phenogenesis, a common variant in our classification system.

Many earlier studies on minor physical anomalies in autism and schizophrenia are hampered by the use of the Waldrop scale [Waldrop et al., 1968] (or a modified version), a short list of 16 minor physical anomalies and their weighted scores, mostly reflecting the findings found in Down syndrome, which limits its value as a checklist for a broad variety of disorders.

Different from the earlier discussed studies on the prevalence of congenital anomalies in pediatric malignancies, in all other studies the investigators did not submit the children to a careful physical examination directed at clinical morphology and so they were only able to detect associations with major anomalies as they were based on the study of death certificates [Miller, 1969], cancer registry records [Narod et al., 1997; Nishi et al., 2000], interviews [Mann et al., 1993; Mertens et al., 1998], and record linkage studies [Windham et al., 1985; Mili et al., 1993a,b; Altmann et al., 1998]. Since major anomalies have a much lower frequency than minor anomalies associations with specific tumors will be more difficult to detect. The only significant relationships observed were the higher incidence of leukemia in children with Down syndrome, and the increased prevalence of brain tumors in children with central nervous system anomalies [Altmann et al., 1998]. In many syndromes, and also in Down syndrome, the diagnosis is rarely based on the accompanying major malformations but rather on the specific pattern of minor anomalies. Indeed most diagnostic indices for Down syndrome use only minor anomalies [Preus, 1977].

An important factor hampering the elucidation of any statistically significant data in earlier studies is the lack of normal values for morphological anomalies in normal children and adults. Only four studies emerge from literature that forms the basis of our current knowledge regarding the epidemiology of morphological anomalies [Marden et al., 1964; Méhes, 1983; Merlob et al., 1985; Leppig et al., 1987]. Lack of standardization of the nomenclature and the absence of uniform diagnostic criteria hinders the comparison of these studies [Frías and Carey, 1996]. A second and even more important drawback is that the studies have been performed in newborn infants only. Several specific anomalies, such as vascular malformations, can be transitory, and minor anomalies can become more or less obvious with age, as the evolution of anomalies in many syndromes has

shown. Especially, only after early childhood the complete phenotype becomes obvious. This implies that many morphological anomalies can be missed in newborn infants. We have concluded, there is a great need for a study in older children or adults focused on the prevalence of mild errors of morphogenesis. Therefore, we are presently planning to study a control group constituted from older children from elementary schools.

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