Quantification of Dysmorphogenesis:
Pattern Variability Index, σ_z

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The pattern variability index (σ_z) is the standard deviation of Z-scored radiogrammetric measurements of an individual expressed relative to norms for age and gender. As applied to standardized measurements of the head and face, a σ_z value of 1.2 approximates the 95th percentile of the normal range of children, adolescents, and adults. Individuals with congenital malformation syndromes tend to exceed 1.2 in the pattern variability index and may achieve values of 1.8–2.0 and above. σ_z thus provides objective indications of dysmorphogenesis and quantification of the degree of departure from the normal appearance.

Many syndromes are discovered and others identified because of the unusual facial appearance of an infant or child. Inelegantly, but perhaps appropriately, the pejorative term "funny-looking kid" has been used to describe craniofacial configurations that are odd in appearance but difficult to define or quantify. Morphologic observations (hypertelorism, low-set ears, inner epicanthic folds) and simple anthropometric measurements (small head circumference, short upper face, etc.) incompletely delineate some of the disproportions that make a given infant, child, or adult appear dysmorphogenic. However, these few measurements and limited observations do not provide a quantitative indication of the degree of departure from normal, that is, the extent to which the appearance is truly "funny."

In this article, we describe a relatively simple measure, the pattern variability index (σ_z) based on standard deviations of sets of Z-scored cranial and facial measurements. The empirical distribution of the statistic σ_z is shown both for normal children and adults and for those exhibiting several dysmorphogenic states and congenital malformation syndromes.

The basis of the pattern variability index (σ_z) is radiogrammetric in nature and involves comparisons with craniofacial distances or dimensions recently published by us [1]. While this new measure has been validated in conjunction with this published compendium of craniofacial dimensions by age and gender, it is applicable in principle to other sets of norms or standards [2]. Indeed, a pattern variability index can be applied to the hand or other body parts and is in no way restricted to the craniofacial skeleton [3].

Materials and Methods

This study is based upon radiogrammetric measurements derived from over 1500 standardized lateral skull radiographs of children, adolescents, and adults. A 60 inch (152 cm) focal-film distance was used throughout, and uniformity of positioning was assured by the use of an orthodontic cephalostat in every case.

The first series, used in the generation of normative values, comprises 1248 orthodontically untreated clinically normal children and adolescents who participated in the University of Michigan longitudinal studies [1, 4]. This sample was largely of Northwest European ancestry and was limited to one child/gender/family. The second sample of 166 individuals included both parents and their adult offspring residing in the Ann Arbor area [5]. The third sample

Received March 22, 1984; accepted after revision October 29, 1984.

This work was supported by National Institutes of Health grant DE 03610.

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AJR 144:365–369, February 1985
0361–803X/85/1442–0365

comprised 31 families of cleft palate propositi, including parents, unaffected siblings, and both affected and unaffected twins [6]. From this latter sample, a series of identified congenital malformation syndromes was also drawn.

Representative cranial and facial distances were computer-calculated from landmarks that had been digitized with an on-line Summagraphics digitizer. These distances were selected to include the most used measurements of the skull, skull base, face, and mandible and have been described by us in detail along with the appropriate age standards [1].

For each craniofacial measurement from each subject, a standardized Z score was computer-calculated as the difference between the measurement and mean for age and gender divided by the age-appropriate standard deviation, that is, $Z = (x - \bar{X})/SD$. Then the standard deviation (σ) of the set of Z scores for each individual was computer-calculated in the customary way, that is, $\Sigma(Z^2/N) - (\Sigma Z/N)^2$. The resulting value was the pattern variability (σ_z) automatically corrected for age and gender and indicative of the extent to which the individual was dimensionally more variable than might be expected. Actual values of σ_z ranged from near the theoretical minimum 0.0, through 1.27 for the most extreme of the normal individuals (fig. 1), to 2.0 and above for malformation conditions.

Data analysis included the calculation and comparison of percentiles of σ_z for the normative series of children and adolescents at each age, for the adult normal series, and for the cleft-palate series of adults, siblings, and affected and unaffected twins. Since appropriate means and standard deviations for age and gender were used in computing the Z scores and σ_z, the effects of age and gender were thus eliminated. However, percentiles of σ_z were first calculated for boys and girls separately, before pooling them in constructing the normative standards. In a similar fashion, possible effects of differences in the number of measurements on σ_z were also considered, as will be described in the next section.

Results

As the first step in data analysis, distributions of the craniofacial pattern variability index (σ_z) were generated for boys

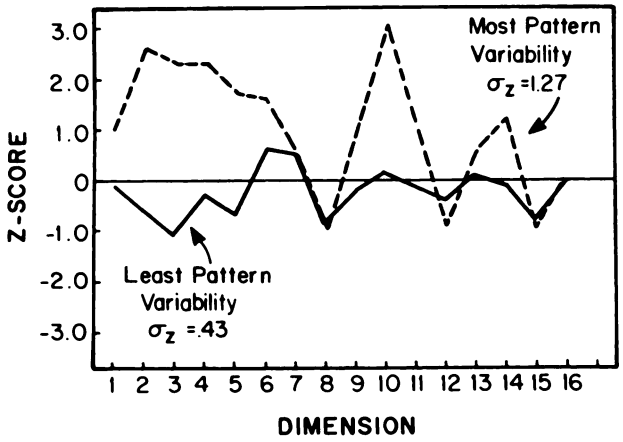

Fig. 1.—Craniofacial pattern profile of individuals with highest and lowest pattern variability indexes (σ_z) in normative series uniformly calculated for 16 craniofacial dimensions. High value of 1.27 reflects combinations of excessively large, medium, and small craniofacial dimensions for age and gender.

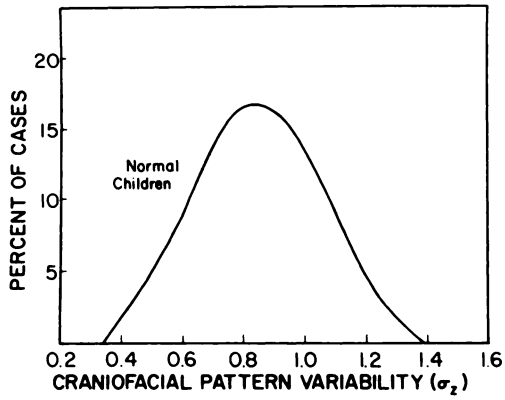

Fig. 2.—Frequency distribution of pattern variability index (σ_z) in normal children of both genders.

TABLE 1: **Percentiles for the Craniofacial Pattern Variability Index (σ_z) in Children and Adolescents**

Age (years)	No.	Percentiles of σ_z				
		5	15	50	85	95
4	26	0.57	0.66	0.87	1.06	1.15
5	53	0.60	0.65	0.84	1.07	1.13
6	105	0.65	0.71	0.86	1.06	1.22
7	110	0.55	0.66	0.83	1.09	1.20
8	129	0.57	0.66	0.81	1.03	1.19
9	122	0.49	0.59	0.81	1.02	1.17
10	132	0.47	0.59	0.84	1.07	1.18
11	108	0.54	0.61	0.78	1.01	1.19
12	120	0.56	0.61	0.79	1.01	1.18
13	98	0.44	0.54	0.77	1.07	1.20
14	108	0.52	0.60	0.77	1.06	1.19
15	64	0.46	0.60	0.74	1.05	1.20
16	43	0.52	0.63	0.81	1.00	1.09
17	30	0.51	0.56	0.77	0.93	1.18
Total (4–17)	1248	0.52	0.62	0.81	1.04	1.18

Note.—These percentiles are based on 13–16 measurements per child (see text) [1].

TABLE 2: **Percentiles for σ_z in a Series of Parents and Their Adult Children**

Group	No.	Percentiles of σ_z				
		5	15	50	85	95
Parents	78	0.60	0.67	0.83	1.05	1.21
Children	88	0.55	0.67	0.79	1.09	1.23
Total	166	0.56	0.67	0.82	1.07	1.21

TABLE 3: **Distribution of the Pattern Variability Index in Cleft-Lip/Cleft-Palate Families**

Group	No.	Percentiles of σ_z				
		5	15	50	85	95
Affected twins*	45	0.63	0.69	1.06	1.40	1.68
Unaffected twins	29	0.61	0.69	0.86	1.11	1.32
Unaffected siblings	78	0.61	0.73	0.88	1.17	1.40
Unaffected fathers	28	0.59	0.64	0.73	0.95	1.06
Unaffected mothers†	31	0.73	0.84	1.00	1.19	1.28

* Distributions significantly different from the unaffected siblings and from the normative distribution of σ_z.
† Significantly different from the normative distribution of σ_z for adults using the Mann-Whitney U test [7].

and girls separately at each age from 4 through 17 years. Since there were no systematic gender differences in those distributions, percentiles for boys and girls were then combined as set forth in table 1. As may be seen, low values of σ_z at each age (corresponding to the 5th percentile) approached the theoretic minimum of 0.0. Very high values of σ_z, approximating the 95th percentile, averaged 1.18–1.20 at most ages. Accordingly, the data from all 1248 radiographs and all 14 ages were then pooled, as also shown in table 1. The resulting distribution of σ_z is depicted in figure 2. The 95th percentile cutoff, corresponding to the upper limits of normal, is thus effectively +1.2 σ_z over the entire range considered and for children and adolescents of both genders. Since some workers may prefer to use the 85th percentile cutoff, this is also given and approximates a σ_z value of 1.05 at all ages.

Inasmuch as σ_z could be affected by the number of craniofacial measurements used, two sets of distributions were generated, one for a set of 13 dimensions per individual and another set for the entire array of 16 Z-scored measurements per subject. Since the two distributions matched closely, it is clear that small differences in the number of measurements do not appreciably affect the magnitude of this index. Moreover, individual comparisons of σ_z at different ages showed reasonably high correlations ($r \geq 0.72$) despite inherent inaccuracies in landmark location, digitizing procedures, and sampling fluctuations affecting the dimensional standards themselves.

In the smaller series of adult individuals (comprising parents and their adult children), distributions of σ_z closely resemble those for the series of children and adolescents described above. Despite dimensional differences and secular change, possible differences in the digitizing procedure, etc., low values of σ_z again approached the theoretic minimum of 0.0 (table 2). High values for adults (corresponding to the 95th percentile) again approximated 1.20 despite the smaller sample sizes.

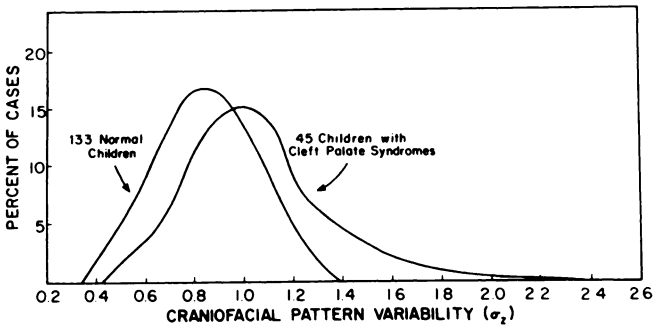

Fig. 3.—Frequency distribution of pattern variability index (σ_z) in 45 cleft-palate (right) and normal (left) children. Boys and girls with cleft palate/cleft lip show systematically elevated values of pattern variability index, attaining or exceeding 2.0 in some cases.

As applied to the extended cleft-palate family series, the upper limits of σ_z tended to be systematically higher than in the normative series, as might be expected (table 3). This is particularly true for the affected twins who greatly exceeded the normal distribution for the pattern variability index (fig. 3). Yet the unaffected twin members and their phenotypically normal siblings also demonstrated an increased proportion of σ_z values in excess of 1.20. Since the use of age- and gender-specific Z scores corrects for overall size differences, such as may be encountered in cleft-palate children, it is evident that the craniofacial pattern variability (σ_z) does identify individuals with unusual or atypical dimensional combinations. It is therefore of interest to note that the clinically normal mothers of cleft-palate twins themselves evidenced an excess of high σ_z values, as shown in table 3. This is consistent with other findings suggesting a gender influence in inheritance of the cleft-palate trait.

In table 4 we deal with the pattern variability index in a subset of the cleft-palate twin series concordant with respect

TABLE 4: **Craniofacial σ_z Values in Monozygotic Twins Concordant for Cleft Lip/Cleft Palate**

Description	Gender	Twin A	Twin B
Pierre Robin	F	1.4	1.4
Otopalatodigital	M	1.2	2.0
Cleft lip	M	1.1	0.8
Cleft lip	F	1.1	0.7
Cleft lip	F	1.5	1.3
Cleft lip	M	1.2	1.7
Cleft soft palate	F	1.1	0.9

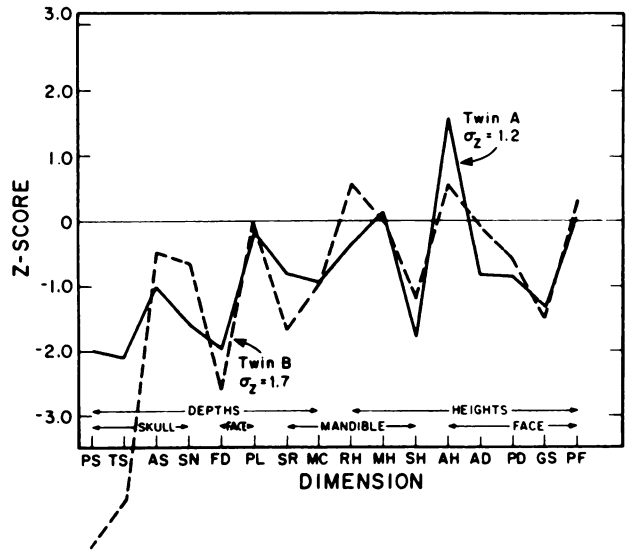

Fig. 4.—Craniofacial pattern profiles in set of twins concordant for cleft lip showing differences in σ_z associated with extent of patterned deviation from normal. High σ_z of 1.7 in twin B is due to extreme shortening of cranial base. For a listing of individual measurements, see Garn et al. [1].

to cleft palate/cleft lip and including two identifiable dysmorphogenetic syndromes. This subset of 14 individuals (seven pairs of concordant monozygotic twins) tends to be higher in σ_z. Eight of the 14 individuals are denoted by craniofacial σ_z values of 1.2 or above, and seven are completely beyond the normal range. Three of four individuals concordant with the Pierre Robin syndrome and the otopalatodigital syndrome are all above the 95th percentile cutoff. This subset further documents the ability of the pattern variability index to identify more extreme examples of craniofacial dysmorphogenesis (fig. 4).

It is therefore apparent that high levels of σ_z, 1.2 and above, do indicate high levels of craniofacial pattern variability. Though individuals with a σ_z value of this amount may be clinically "normal," they are of unusual facial proportions and appearance, compared with the normative group. (Two children with exceptionally high σ_z values exceeding 1.2 and 1.38, respectively, proved to be of Chinese ancestry; therefore, they were dimensionally unlike the normative sample of Northwest European descent). Still higher levels of σ_z, for example, 1.6, 1.8, and above, denote a very high level of pattern variability and may indicate unidentified malformation syndromes.

Discussion

As shown in our extensive study, the statistic σ_z proves to be a useful quantitative measure of the degree of dysmorphogenesis in the head and face. With a well positioned lateral skull radiograph in hand, and with radiogrammetric dimensions measured as we have described earlier, it is now possible to provide in numeric terms the degree of patterned departure from normal. A σ_z value of 1.2 or greater denotes the upper limit of patterned variation in the head and face, though a pattern variability index in excess of 1.0 is suggestive of dysmorphogenesis.

Aside from the radiograph, preferably taken with a cephalostat, the technology required for determining the pattern variability index for an individual is minimal. The measurements can be made with a simple ruler, with a dial-reading caliper, or on a digitizer. The calculations in turn can be made on a desk calculator, many of which are prewired for the calculation of sigma (σ). Standard measurements of craniofacial dimensions in children and adolescents are given in table 2 of Garn et al. [1].

Since the radiogrammetric standards used in the calculations were arranged by 1-year intervals and for males and females separately, neither age nor gender is a problem in the calculation of σ_z. Differences due to physiologic age (bone age or skeletal age) are of little importance here, as are differences in gross size, which simply increase or decrease most of the dimensions. However, greatly advanced maturity or greatly delayed sexual maturity might affect σ_z if age instead of bone age were used.

Though the calculations for each σ_z were generated on an on-line computer, to facilitate the thousands of σ_z values generated, they can be made on a hand-held calculator for each individual once the necessary Z scores are calculated. With a high value of σ_z, suggestive of a malformation condition, attention to the individual Z scores further serves to identify the cranial or facial areas that are most deviant from the average for that individual. This by itself can be helpful in syndrome identification and in considering the needs for plastic and reconstructive surgery. Moreover, the Z scores so computed can be used in calculating the pattern similarity measure in comparisons with known syndromes for syndrome identification [1].

Compared with the distribution of σ_z values in these normal and orthodontically untreated boys and girls and a sample of parents and their adult children, σ_z tends to be considerably higher in known malformation states. This would not be the case in malabsorption states, simple growth failure, or hypopituitarism. Since σ_z is either unaffected or little affected by simple differences in size, nutritional extremes and malabsorption states are not likely to be identified by this measure.

The question of syndrome identification is not the purpose of this article, having been dealt with previously in relation to the pattern similarity measure (r_z) using Z-scored dimensions [1]. Rather it does involve a method of determining the excess

of dimensional variability in the face and head of a child or adult. The greater the dimensional variability (σ_z), the more unusual the craniofacial configurations are relative to the group and the greater the possibility of a malformation syndrome. For patients who appear to be "funny," this is a first step in quantification, supporting or rejecting purely visual impressions and to be added to anthroposcopic observations on the ears, nose, eyelids, and lips.

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