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Applications of the Pattern Variability Index (σ_z) to the Quantification of Dysmorphogenesis in the Hand

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We have generated percentiles for the pattern variability index (σ_z) of the hand in 1,088 normal infants, children, and adults and have analyzed pattern variability indices for 820 individuals representing 50 congenital malformation syndromes with respect to the normal percentiles. The majority of the affected individuals exhibited elevated σ_z values for the hand, some vastly in excess of normal, while such syndromes as Down, Turner, and the Prader-Willi syndrome were low rather than high in pattern variability of the hand.

Key words: dysmorphogenesis, pattern variability index, σ_z, quantification, hand skeleton, metacarpals, phalanges

INTRODUCTION

Over the years various attempts have been made to quantify the degree of dysmorphogenesis so as to compare affected members of a lineage with each other or one malformation syndrome with another. Some workers have used checklists or stigmata counts, including such characteristics as low-set ears, sloping foreheads, hypertelorism, the transverse palmar crease, camptodactyly, brachydactyly, etc. Other investigators have made use of anthropometric measurements and ratios or proportions, such as span relative to stature.

Still others have made use of measurements of the bones of the hand skeleton, so as to include angles (such as the carpal angle), relative lengths of various metacarpals (the metacarpal sign) and other bone-to-bone ratios. These approaches, while useful, have failed to make use of the very large amount of metric information

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inherent in the hand skeleton or even the 19 tubular bones that are most easily measured on properly positioned postero-anterior hand radiographs.

Recently, we have introduced a simple measure of dysmorphogenesis applicable to the head and face, which we have called the pattern variability index [Garn et al, 1984, 1985]. Calculated as the standard deviation of craniometric measurements, previously converted into Z-scores, normalized for age and sex, this measure (symbolized as σ_z) has several advantages. First, it expresses the degree of dysmorphogenesis as a single number, ranging from nearly 0.0 to 3.0 and above. Second, the pattern variability index is easily calculated. Third, σ_z is easily understood, being the measure of pattern variability. Fourth, it is independent of size and is therefore applicable to dwarfism and gigantism. If follows that the pattern variability index or σ_z should be particularly applicable to the hand skeleton since norms or standards for metacarpal and phalangeal lengths are already established in the literature.

Here, we have given attention to the pattern variability index (σ_z) for the hand, using both a reference sample of 1,088 clinically normal individuals and a syndrome sample of 820 individuals representing 50 different malformation syndromes. In so doing, we have attempted to provide both percentiles of σ_z, based on normal individuals previously described in the literature and values for σ_z and the distribution of σ_z in a very sizeable dysmorphogenic series. With the latter series and in comparison to the "normal" distribution of σ_z, it is now possible to evaluate the use of this radiogrammetrically derived measure to quantify the extent of patterned variability or dysmorphogenesis in the hand skeleton separate and apart from bone size per se.

MATERIALS AND METHODS

This study is based upon radiogrammetric metacarpal and phalangeal length measurements of 1,088 clinically normal subjects and 820 individuals with congenital malformations, chromosomal abnormalities, or single-gene substitutions.

The normal subjects were all participants in the Fels (Institute) longitudinal studies and comprise the same group of individuals employed in the metacarpophalangeal length standards previously published by us. Those participants with evidences of dysmorphogenesis (including synphalangism, club foot, growth delay, etc.) were excluded from the database and from the individual calculations of σ_z reported in this study [Garn et al, 1972].

The syndrome population, involving some 50 syndromes, included such common malformation syndromes as Down syndrome and such uncommon syndromes as the De Lange syndrome. Sample sizes for each of these syndromes, numbering from 232 downward, are given in Tables I–IV. For further description of the syndrome population see Poznanski [1984a,b].

Starting with the radiogrammetric length measurements on 19 metacarpals and phalanges per individual (from Met I through Distal V), each raw measurement was then converted into a corresponding Z-score (Z) or standard deviation unit, appropriate for age and sex, using means and standard deviations previously published by us [Garn et al, 1972; Poznanski, 1984a]. These conversions were originally made on an IBM 3600 computer and stored on magnetic tape. Having made the conversion of raw scores to Z-scores, the statistic σ_z was then calculated for each individual in the normal (or reference) population and each individual in the syndrome sample using

the Amdahl 5860 computer at The University of Michigan. The statistic σ_z for each individual is of course

$$\frac{\Sigma Z^2}{N} - \left(\frac{\Sigma Z}{N}\right)^2$$

or the root mean square (RMS) deviation of Z from the individual's mean Z. σ_z is therefore independent of the size of individual bones, which is separately indicated by the mean Z ($\overline{Z}$).

Having calculated σ_z (the pattern variability index) for each individual, the centile distribution of σ_z was then calculated for the entire sample of normal children and adults and for normal males and females separately, to test for possible sex differences and age effects. Combined sex and combined age centiles of σ_z were then calculated, deriving the 5th, 15th, 50th, 85th, and 95th centiles because of their clinical utility.

Mean σ_z values were similarly calculated for each syndrome sample (from the mean age and sex-corrected values of Z) as well as complete distributions of σ_z for some of the larger and more interesting syndrome groups. These mean values of σ_z syndrome by syndrome, and illustrative distributions of σ_z in normal individuals and in syndromes, are given in the tables and figures that follow.

It should be noted that the reference or normal population is an American-born population of northwestern European origin and may therefore be inappropriate as a reference population for comparison with individuals of other origins.

FINDINGS

In the first step of data analysis a complete set of centiles for σ_z (5th through 95th) was calculated for the normal children, using 2-year age groupings, and for normal adults, to test for possible age trends in the pattern variability index. No

TABLE I. Sex Differences in Centile Values for the Pattern Variability Index (σ_z) of the Hand

		Percentiles for σ_z				
Sex	N*	5	15	50	85	95
Males	554	0.339	0.396	0.533	0.732	0.860
Females	534	0.275	0.328	0.456	0.657	0.822
Combined	1,088	0.296	0.358	0.498	0.691	0.834

*Based on 18 metacarpals and phalanges excluding metacarpal 1, throughout.

TABLE II. Effect of the Number of Bones on Centile Values of σ_z

No. of bones	No. of cases*	Percentiles for σ_z				
		5	15	50	85	95
17	1,088	0.296	0.358	0.498	0.691	0.834
18	1,088	0.303	0.358	0.494	0.687	0.832
19	1,084	0.305	0.363	0.495	0.684	0.813

*Sample Ns maximized to eliminate sampling effects.

systematic age trends were found, so further analyses centered on σ_z distributions for the entire normative sample of 554 males and 534 females with a sex ratio of 1.04:1.00.

When the pattern variability index for the hand was next calculated for males and females separately, as shown in Table I, all centile values of this index for males were slightly higher than the corresponding centile values for females. Across the centiles, 5th through 95th, values of σ_z for males exceeded those for females by 0.05 on the average, or very close to 10% overall. However the combined-sex σ_z values, also shown in the first table, were agreeably close to both of the sex-specific centiles and may therefore be employed for most purposes. Table I, then, provides male centile standards, female centile standards, and the combined-sex standards for σ_z as applied to the hand skeleton.

The question of the impact of the number of bones on the magnitude of σ_z and its distribution was next investigated, using different numbers of bones and different combinations of bones, from a maximum of 19 down to a minimum of 10. As shown in Table II, the number of bones (17–19) had no impact on the centiles for this measure. Further analyses, reducing the number of bones considered to 16, 15, 14, and even 10 showed virtually no effect of bone number on values of σ_z as long as sample Ns were maintained (Fig. 1). While missing rays or missing rows may well exclude the calculation of σ_z for any given individual, a few metacarpals or phalanges excluded because of incomplete or missing measurements should not bias the results.

From these preliminary steps in generating and exploring centiles of σ_z for the hand in over 1,000 clinically and morphologically normal individuals, we may therefore center upon the sex-specific centiles given in Table I and the combined-sex centiles in Tables I and II. The mean combined-sex value of σ_z is very close to 0.50, the 85th centile is nearly 0.70, and the 95th centile is 0.83. The complete distribution of σ_z for the hand in the normal population is therefore shown in Figure 2 for reference.

In the next step we calculated values of σ_z for a total of 50 syndromes, including both those with larger sample sizes (10 through 232), and those based on smaller samples down to as little as one for a single syndrome (hypophosphatasia). These values of σ_z, based upon mean sex-appropriate and age-appropriate Z-scores, ranged downward from a maximum of 3.24 in Carpenter syndrome to a minimum of 0.29 (for the Prader-Willi syndrome). In most of the syndromes, however, values of σ_z exceeded the 85th centile for normal and, in all but seven of the syndromes (14%), σ_z exceeded the 50th centile for normal individuals (Figs. 3, 4).

Table III presents values of σ_z for 18 syndromes involving ten subjects or more. For some of them σ_z far exceeded the 50th centile of the normal distribution by many SDs (taking the SD of σ_z as 0.2 in normal individuals). Most of the syndromes so analyzed greatly exceeded the mean value of σ_z for normal individuals. However, four syndromes (Turner, Marfan, Multiple epiphyseal dysplasia, and the Prader-Willi) were demonstrably low in σ_z. It will also be noted that most of the syndromes considered had negative (minus) values of mean Z, ie, the metacarpals and phalanges were short, in some cases as much as 5 SD below normal. Clearly, having short metacarpals and phalanges for age and sex does not mitigate against the possibility of a high σ_z (or pattern variability) nor does large or long fingers (as in Sotos syndrome) produce an elevated value of this measure.

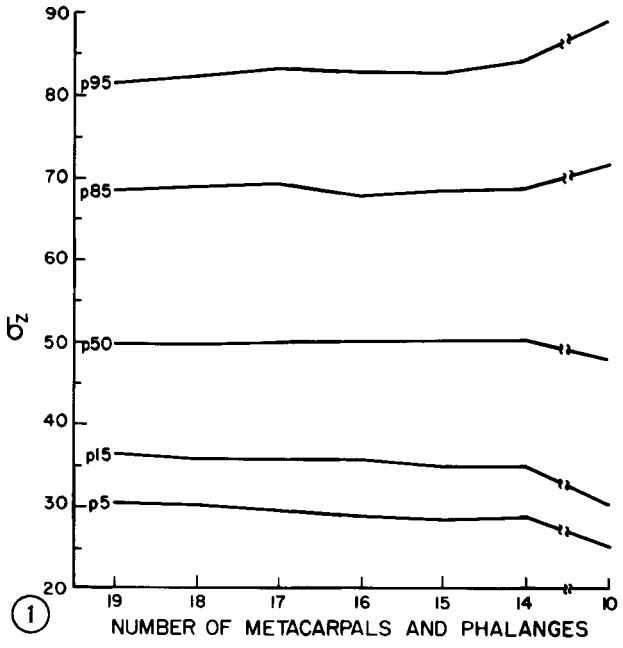

Fig. 1. Relationship between the number of bones included in the calculation of σ_z and centiles for the pattern variability index in 1,084 clinically normal children and adults. As shown, cumulatively eliminating metacarpal 1, metacarpal 5, distal 5, distal 1, proximal 4, and then mid 3–5 proximal 5 has little effect on the distribution of this measure of skeletal dysmorphogenesis.

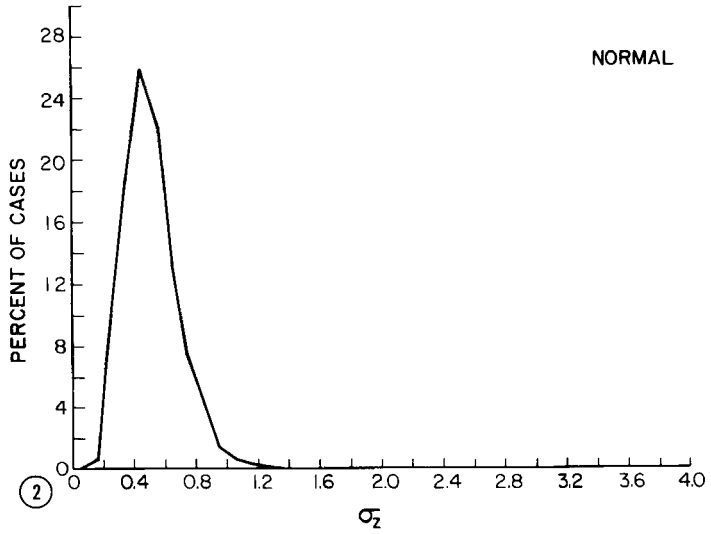

Fig. 2. Frequency distribution of the pattern variability index (σ_z) for the hand in 1,084 clinically normal White infants, children, and adults. In normal individuals the distribution of σ_z is only slightly skewed (SK 1.43) and σ_z values of 0.69 and 0.83 correspond to the 85th and 95th centiles of the combined-sex distribution.

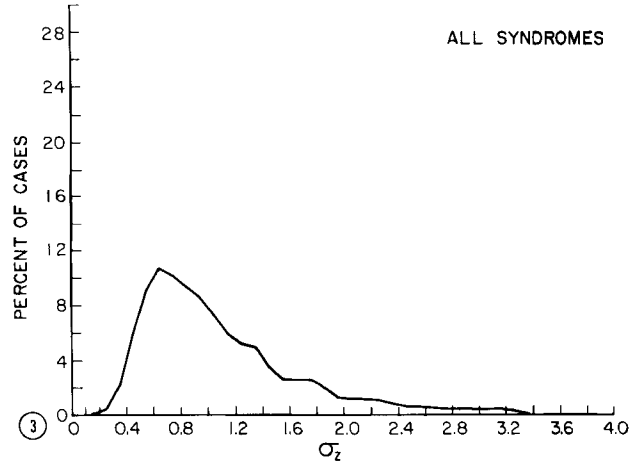

Fig. 3. Frequency distribution of σ_z for the hand in a very large pooled sample of dysmorphogenesis syndromes. While some of the individuals characterized have low values of σ_z, affected individuals in general have elevated σ_z values, in some cases far beyond the upper levels of normal. See Tables III and IV for individual syndromes.

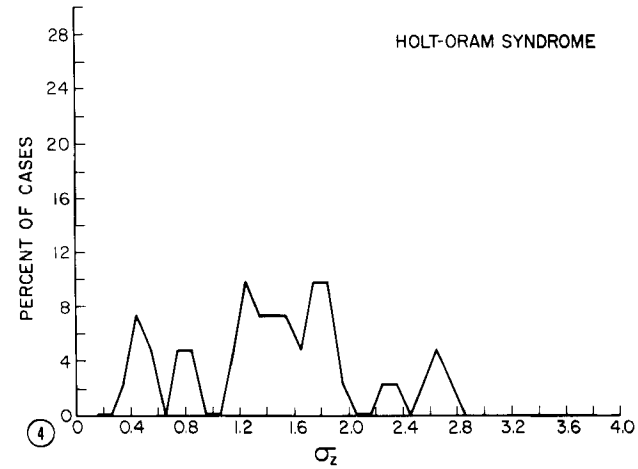

Fig. 4. Smoothed distribution of σ_z (the pattern variability index) for the metacarpals and phalanges of individuals with the Holt-Oram syndrome. Though a few of the affected cases fall below the average σ_z for normal individuals (0.5), the majority exceed the highest σ_z values found in over 1,000 normal individuals.

Finally we list the values of σ_z and the mean Z for all 50 syndromes considered, here again presented in *decreasing* order of magnitude of σ_z (Table IV). Again it will be noted that most of the syndromes are characterized by elevated values of σ_z, above the 85th centile for normal in 29 cases (58%), and above the mean value for σ_z in normals in 43 examples (86%). Clearly the extent of abnormality in the relative proportions of the metacarpals and phalanges is very considerable in the majority of the syndromes considered, in some cases as much as 13 SD above the mean σ_z for normals, and even as much as 11 standard deviations above the 95th centile for

TABLE III. Metacarpophalangeal σ_z Values for Syndromes Characterized by Numbers of 10 and Above

Syndrome*	N	Mean Z	σ_z
Diastrophic dysplasia	25	−3.310	1.598
Mucopolysaccharidosis IV	18	−3.273	1.504
Holt-Oram	19	−0.653	1.386
Achondroplasia	79	−3.247	1.134
Mucopolysaccharidosis I-H	21	−0.526	1.260
Cleidocranial dysplasia	15	−1.558	1.021
Hand-foot-genital	14	−0.958	1.017
Pseudoacondroplastic dysplasia	22	−5.43	1.015
Tricho-rhino-phalangeal	11	−1.663	0.932
Pseudohypoparathyroidism and PPHP	46	−2.284	0.912
De Lange	20	−5.247	0.731
Oculo-palato-digital	23	0.995	0.600
Sotos	11	3.526	0.584
Down	232	−2.968	0.506
Turner	35	−1.526	0.482
Marfan	23	1.305	0.424
Multiple epiphyseal dysplasia	29	−1.053	0.315
Prader-Willi	17	−2.211	0.292

*Nomenclature following Birth Defects Series and Bergsma [1979].

normal. On the other hand, there are syndromes including Turner, Marfan, and the Prader-Willi syndrome where the extent of metacarpophalangeal malformation is very low, even by normal standards. It will be noted that syndromes with large or long metacarpals (Frontometaphyseal dysplasia, the Kniest syndrome, the Oto-palato-digital syndrome, Sotos syndrome, and Marfan syndrome) are spread over the range of σ_z values, from extremely high (1.838) to average (0.482), so that hand size is not a factor in the magnitude of σ_z. Correlations between mean Z and σ_z are effectively zero, further attesting to this point.

It is evident, therefore, that most syndromes are characterized by elevated values of σ_z for the hand, confirming the extent of dysmorphogenesis previously shown by the pattern profile approach and what was, in many cases, intuitively obvious to the experienced radiologist. A high value of σ_z, exceeding the 95th centile of normal (0.834), does suggest the presence of a congenital malformation syndrome and is an alerting value. However, not all syndromes are dysmorphogenic in the hand skeleton. Some are quite close to average in the degree of patterned variability (though not in bone size). The Prader-Willi syndrome (for which we have 17 cases) has minimal metacarpophalangeal dysmorphogenesis, despite the extremely small size of the metacarpals, proximals, middles, and distals. In this sense, and in respect to σ_z, the hand in the Prader-Willi syndrome is not dysmorphogenic!

DISCUSSION

As demonstrated in this large normative and comparative study, the pattern variability index (σ_z) is a useful measure of the degree of dysmorphogenesis in the hand skeleton. It is applicable to infants, children and adults, assuming the availability

TABLE IV. Complete List of Metacarpophalangeal σ_z Values Arranged by Decreasing Order of Magnitude

Syndrome	N	Mean Z	σ_z*
Carpenter	3	−1.684	3.240
Apert	3	−0.516	3.080
Hypophosphatasia	1	−6.521	1.979
Asphyxiating thoracic dysplasia	2	−3.630	1.948
Frontometaphyseal dysplasia	4	2.479	1.838
Coffin-Siris	3	−4.511	1.737
Salino-Mainzer	8	−2.016	1.653
Chondroectodermal dysplasia	7	−4.521	1.624
Diastrophic dysplasia	25	−3.310	1.598
Mucopolysaccharidosis IV	18	−3.273	1.504
Ruvalcaba	4	−3.784	1.493
Campomelic dysplasia	3	−1.532	1.486
Holt-Oram	19	−0.653	1.386
Kniest	4	0.379	1.296
Mucopolysaccharidosis I-H	21	−0.526	1.260
Seckel	2	−6.730	1.174
Achondroplasia	79	−3.247	1.134
Metaphyseal chondrodysplasia, McKusick	8	−5.647	1.080
Acrodysostosis	3	−6.074	1.079
Cleidocranial dysplasia	15	−1.558	1.021
Hand-foot-genital	14	−0.958	1.017
Pseudoachondroplastic dysplasia	22	−5.430	1.015
Mucopolysaccharidosis VI	5	−1.395	0.976
Mucolipidosis III	5	−1.105	0.972
Larsen	6	−1.300	0.939
Tricho-rhino-phalangeal	11	−1.663	0.932
Pseudohypoparathyroidism and PPHP	46	−2.284	0.912
Laron dwarfism	5	−4.921	0.858
4p-	5	−4.900	0.801
De Lange	20	−5.247	0.781
Metaphyseal chondrodysplasia, Jansen	3	−3.337	0.765
HGH dwarfism	7	−3.458	0.720
Fibrodysplasia ossificans progressive	5	0.000	0.695
Mucopolysaccharidosis I	7	0.111	0.641
Metatropic dysplasia	4	−1.979	0.628
Nevoid basal cell carcinoma	4	−0.226	0.626
Mucopolysaccharidosis I-H/S	6	0.284	0.605
Oto-palato-digital	23	0.995	0.600
Sotos	11	3.526	0.584
Silver	2	−1.632	0.571
Hypochondroplasia	23	2.221	0.528
Down	232	−2.968	0.506
18q-	3	−3.560	0.505
Turner	35	−1.526	0.482
Marfan	23	1.305	0.424
Cockayne	6	−4.633	0.399
Mucopolysaccharidosis I-S	3	−0.547	0.366
Metaphyseal chondrodysplasia, Schmid	6	−1.005	0.341
Multiple epiphyseal dysplasia	29	−1.053	0.315
Prader-Willi	17	−2.211	0.292

*Calculated from the mean Z for each of the digital segments for each syndrome.

of reference standards for metacarpal and phalangeal lengths and can even be applied to fetal hand sections, using the techniques we have previously described [Garn et al, 1975]. A σ_z value of 0.70 or higher is at least borderline with respect to dysmorphogenesis in the tubular bones of the hand, a value of 0.83 or higher is at or above the 95th centile of normal, and individuals with a pattern variability index for the hand at 1.00 and higher certainly merit further clinical investigation.

σ_z has numerous advantages in the study of congenital malformation syndromes. It is easy to understand, being the RMS (root mean square) deviation from the mean of sex-specific and age-appropriate *Z*-scored metacarpal and phalangeal measurements. It is easy to calculate, at a computer terminal or with a programmable calculator, by any worker familiar with the SD (σ). It is not much affected by missing or incomplete measurements so that the full number of 19 metacarpals and phalanges is not essential. Finally it can be applied to individuals of either sex or to those of indeterminant sex.

As shown by the 50 syndrome groupings analyzed, the majority of dysmorphogenesis states are characterized by elevated σ_z values, many of them far beyond the borderlines of normal metacarpophalangeal pattern variability. Values of σ_z for individual syndromes are intuitively reasonable when the listing of high σ_z values is reviewed, though further questions arise when clinically normal individuals with high σ_z values are encountered. However, not all syndromes are characterized by elevated values of the pattern variability index, and both Down syndrome and Turner syndrome are low with respect to σ_z in the hand.

In theory, individuals with unusually large hands for sex and age might be characterized by elevated σ_z values, simply because all of the Z-scores for metacarpals and phalanges are high. However, the mean σ_z for Sotos syndrome and Marfan syndrome are not elevated. Conversely, growth delays and dwarfism might be associated with low σ_z values, but the various kinds of dwarfism and delay reviewed here alleviate this concern.

As with the pattern similarity index (r_z) the measure σ_z can also be used in family-line studies and in extended lineages. Given a propositus with a high σ_z and a yet-undefined syndrome, a similarly high σ_z for one parent is at least suggestive. Comparably high σ_z values for siblings or other relatives do suggest that they are affected members, in which case r_z should also be applied [Poznanski, 1984a,b]. σ_z measures the degree of patterned departure from normal, not its type, and there are lineages with more than one congenital malformation syndrome.

Now the reference standards for metacarpal and phalangeal lengths previously published by us [Garn et al, 1972; Poznanski, 1984a] and the normative centiles of σ_z given in this paper are derived from White children of northwestern European origin. They are not directly appropriate for Blacks (who have longer metacarpals and phalanges) or Japanese or Puebloans (who have shorter tubular bones of the hand). However, σ_z and the metacarpal and phalangeal length norms may be used for most individuals of European descent, with some caution.

In short, the pattern variability index (σ_z) is a measure of dysmorphogenesis, using a large number of discrete length measurements normalized for sex and age in its computation. It could be applied to the metatarsals and other tubular bones of the foot or to other bones in the axial and appendicular skeleton, given normative information on the dimensions of those bones.

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