Published in final edited form as:

Am J Phys Anthropol. 1986 June ; 70(2): 195–201. doi:10.1002/ajpa.1330700206.

Metacarpophalangeal Pattern Profile Analysis in Clinical Genetics: An Applied Anthropometric Method

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Abstract

The hand is a complex anatomical structure with the component bones susceptible to a combination of environmental and genetic factors that may affect the bone length and width. The alterations may involve a single bone or specific group of bones. The metacarpophalangeal pattern profile (MCPP) developed by Poznanski, Garn, and others (Poznanski et al. Birth Defects VIII (5): 125–131, 1972) is a graphic representation of the relative lengthening and shortening of the 19 tubular bones of the hand useful for diagnosis, comparison of dissimilar patients, and gene carrier detection. The profile hand bone measurements are derived from posteroanterior hand radiographs and are standardized for age and sex. Specific profiles have been developed for several syndromes. Therefore, MCPP analysis has developed from a method of describing changes in the hand to a technique useful in assigning a diagnosis to a specific syndrome and evaluation of skeletal development. The current status of MCPP analysis in clinical genetics, particularly with the Prader-Labhart-Willi and Sotos syndromes, is discussed.

Keywords

Prader-Labhart-Willi syndrome; Sotos syndrome; Discriminant analysis; Correlation studies

Metacarpophalangeal pattern profile analysis (MCPP) is an application of an anthropometric technique that has been utilized increasingly in clinical genetics to evaluate individuals with a variety of congenital malformation syndromes. A number of biological anthropologists were instrumental in the development and application of this method (Garn et al., 1972). More recently a number of investigators have broadened the analysis of hand bone lengths by applying multivariate statistical methods in an effort to provide an additional diagnostic tool for certain disorders (Landry et al., 1979; Butler et al., 1982).

The hand is a complex anatomical structure. There are 28 component bones susceptible to a combination of factors (e.g., environmental and genetic) that may alter length and width.

The alterations may involve a single bone or specific group of bones in a digit (e.g., Holt-Oram syndrome) or within a row of bones such as the metacarpals (Proger et al., 1968; Poznanski et al., 1970). There are syndromes in which non-homologous segments of the hand are affected and others characterized by size reduction of a single segment such as the middle phalanx of the fifth digit (Garn et al., 1972).

Investigators in the past have attempted to examine specific hand bones in syndromes, for example, Down syndrome and the “metacarpal sign” or gradient of metacarpal shortening in Turner syndrome described by Archibald et al. (1959). Ratios of length and width of major hand bones have also been examined in Marfan syndrome and other connective tissue disorders (Parish, 1967).

These methods were helpful in certain conditions, but there was a need to describe the overall relationship of the hand bone lengths. Subtle changes may be detected by examining the overall relationship that may be overlooked in the routine radiological hand examination. An MCPP was developed by Garn et al. (1972) and Poznanski et al. (1972a) as an approach to the above problems. MCPP analysis is a graphic method of depicting lengthening and shortening of the tubular hand bones and their relationship to one another (Poznanski et al., 1972a). The hand bone lengths used for the profile are measured from posteroanterior radiographs and converted to Z scores from established bone length standards for age and sex (Garn et al., 1972; Poznanski, 1974). MCPP analysis as a tool for diagnosis has been applied to several syndromes as represented by published profiles in Table 1. Several of these syndromes have specific patterns that are easily recognized, while other patterns are not as striking and detailed statistical analysis is required before clinical application.

We have recently derived a method of MCPP analysis for the Prader-Labhart-Willi and Sotos syndromes to evaluate the potential of this technique to serve as an additional diagnostic criterion, particularly for the younger patient.

MATERIALS AND METHODS

Posteroanterior hand radiographs were obtained for 38 individuals (23 males and 15 females with an age range from 0.2 to 38.5 years and a mean age of 12.2 years) whose clinical features (neonatal hypotonia, neonatal feeding problems, delayed developmental milestones, mental retardation, obesity [87% of individuals with triceps skinfolds > 85th percentile], small hands and feet, hypogonadism and chromosome 15 deletions [54% of individuals]) were consistent with the diagnosis of Prader-Labhart-Willi syndrome (PLWS). Therefore, two PLWS groups were identified, with 20 individuals and the chromosome 15 deletion in one group and 18 individuals with normal chromosomes in the second group.

Posteroanterior hand radiographs were also obtained for 16 individuals whose clinical features (large size at birth, large hands and feet, macrocephaly, downslanting palpebral fissures, hypertelorism, poor coordination, and variable mental retardation) were consistent with the diagnosis of Sotos syndrome. This group included 11 males and 5 females ranging in age from 0.8 to 13.8 years, with a mean age of 5.4 years.

The metacarpophalangeal bone lengths of each subject were measured to the nearest 0.1 mm with a vernier caliper and compared to bone length standards appropriate for age and sex (Garn et al., 1972; Poznanski, 1974). Through these comparisons, Z score values for the 19 bones of each subject were obtained (Z score = observed bone length minus mean bone length divided by the standard deviation associated with the particular age and sex of normal standards). The MCPP for a given individual is, therefore, the set of 19 Z scores, which may be plotted on a graph or subjected to various statistical methods for study and comparison with the MCPP of other individuals or groups of individuals.

A mean pattern profile, based on the average Z score for each bone of the individual, was derived. The pattern of each individual was compared to the group mean pattern via a correlation program which produces Pearsonian r values.

A forward stepwise method of discriminant analysis was performed on the 19 Z scores and age for the individuals with Prader-Labhart-Willi or Sotos syndromes and a control group of 41 normal subjects whose hand radiographs were randomly obtained from the records of Indiana University School of Dentistry, Department of Orthodontics. The sample of 41 control subjects included 17 males and 24 females, with an age range of 9.5 to 18 years and a mean age equal to 13.1 years. The purpose of applying the discriminant method was to discover whether a smaller combination of variables would clearly separate groups of affected individuals from normal subjects, thus providing an easily applied diagnostic tool for the clinician evaluating a patient suspected of having one of these disorders.

RESULTS

Figure 1A presents the mean pattern profile based on the 38 individuals with Prader-Labhart-Willi syndrome. It is essentially flat with no obvious vertical deviations. The mean Z scores fall between −1.7 and −2.3. Therefore, each hand bone was significantly shorter than normal at the 5% level. From the profile, it appears that the distal hand bones are shorter than the proximal bones. The mean Z scores of the two groups of PLWS individuals based on the chromosome results (deletion or nondeletion) showed two separate profiles (Fig. 1B). An obvious separation of the two profiles exists when comparing the metacarpals, but there is overlap for the remaining bones.

The Pearsonian r test to assess similarity between the individual patterns and their group mean reveal 14 of 20 members of the deletion chromosome group and seven of 18 nondeletion members with a significant positive correlation at the 5% level. Thus, the deletion chromosome group appears more homogeneous, which contrasts with the heterogeneity of the nondeletion group.

A stepwise discriminant analysis of all 38 PLWS and 41 control individuals resulted in a correct classification rate of 96.2%. This discriminant function was based on three of the 19 hand bones plus age. The three MCPP variables in the discriminant function were Z scores representing (1) the fifth distal phalanx, (2) the fifth middle phalanx, and (3) the fifth metacarpal. Therefore, all of the discriminating variables between the control and PLWS individuals were of the fifth finger.

The mean pattern profile based on the 16 individuals with Sotos syndrome contains one major peak in the proximal phalangeal area (Butler et al., 1985). The mean Z scores fall between 1.5 and 3.5. Any Z score of 0.5 or higher is significantly different from zero; therefore, each hand bone is significantly longer than the mean for normal individuals at the 5% level. From the profile, it appears that the distal hand bones are relatively short compared with the proximal bones. Next, the correlation program was used to assess similarity between the mean pattern and the pattern of each of the 16 individuals. A significant positive correlation was found in 12 of the 16 individuals.

Discriminant analysis of the normal and Sotos syndrome cases resulted in a discriminant function based on two of the 19 MCPP variables plus age (Table 2). In the discriminant analysis, patients with Sotos syndrome were distinguished from the normal control group at an overall correct classification rate of 100% for our sample.

DISCUSSION

The small and large hand sizes in Prader-Labhart-Willi and Sotos syndromes, respectively, are well known clinically. The mean pattern profiles based on the individuals we have studied confirm these impressions in quantitative terms.

Hand pattern profiles should not change with age, although the influence of certain factors (e.g., malnutrition) on the hand profile is not known (Hayes and Say, 1977). Thus metacarpophalangeal pattern profiles of affected individuals have shown good consistency from one age to another in normal individuals and in subjects with recognized syndromes (Hayes and Say, 1977).

The results of discriminant analysis suggest that effective classification of PLWS and Sotos syndrome indivduals compared with normal individuals on the basis of MCPP data is possible. These observations suggest the potential of this multivariate statistical method in the evaluation of patients in whom either Prader-Labhart-Willi or Sotos syndromes are suspected. The advantage of discriminant analysis is the possibility that group separation will be maximized on the basis of two to three hand bone lengths alone, thus providing all the information needed to separate affecteds from normal. A suspected patient’s D score value for these variables could then be entered into the linear equation to determine whether the individual’s discriminant score falls within the range of scores for affected individuals. Poznanski (1984) has emphasized the superiority of discriminant analysis in correctly classifying affected and normal individuals as compared with correlation studies. Similarly he stressed the potential of multivariate statistical methods for improving the recognition of similarities and differences between patterns.

Discriminant analysis was also used by Landry et al. (1979) to separate hand patterns among several syndromes (Down, Turner, achondroplasia, and normal). Their analysis of the MCPP data resulted in approximately 20% improvement in classification over the use of correlation studies (Landry et al., 1979). Their results suggested that certain congenital malformation syndromes may be grouped with good accuracy on the basis of MCPP data, and encouraged

the development of an automated system for pattern recognition in the diagnosis of certain syndromes.

Discriminant analyses of MCPP data of other syndromes have been undertaken. Kaler et al. (1982) examined MCPP data from individuals with Crouzon syndrome with a stepwise forward discriminant analysis program. They found that these individuals could be discriminated from a normal control population with a correct classification rate of 88.3% by the use of only three of the 19 MCPP variables. Although the Crouzon syndrome hand is considered radiologically normal, subtle differences were identified via discriminant analysis of MCPP data that may have been overlooked with correlation studies.

Not only may MCPP analysis be used as a diagnostic tool, but it may have value in nosology. Kaler et al. (1982) found high correlations (+0.69 to +0.88) when comparing mean pattern profiles of individuals with Crouzon, Pfeiffer, and Carpenter syndromes. On the basis of the hand profile studies, they suggested there may be a common developmental mechanism, varying in extent, which acts on the hand skeleton in each of the three (Crouzon, Pfeiffer, and Carpenter) genetically distinct craniosynostosis syndromes.

The role of physical anthropologists such as Stanley Garn and others in the development and application of hand profiles should be emphasized. MCPP is an anthropometric method of demonstrated value in medical genetics, representing a salient example of the contribution that applied biological anthropology may lend to clinical medicine.

Acknowledgments

The authors wish to thank Drs. Rebecca Wappner, Bryan Hall, Patricia Bader, and Andree Walczak for allowing us to evaluate their patients. This research was supported by PHS-5T32 GM07468 (M.G.B.) and PHS-T32 DE07043 (F.J.M. and S.G.K.). The authors acknowledge use of the facilities of Computing Services, Indiana University-Purdue University at Indianapolis. An earlier version of this paper was presented in the symposium “Application of Anthropological Methods in Medical Genetics” on April 12, 1984 at the 53rd Annual Meeting of the American Association of Physical Anthropologists, Philadelphia. We thank Judy Copeland for expert preparation of the manuscript.

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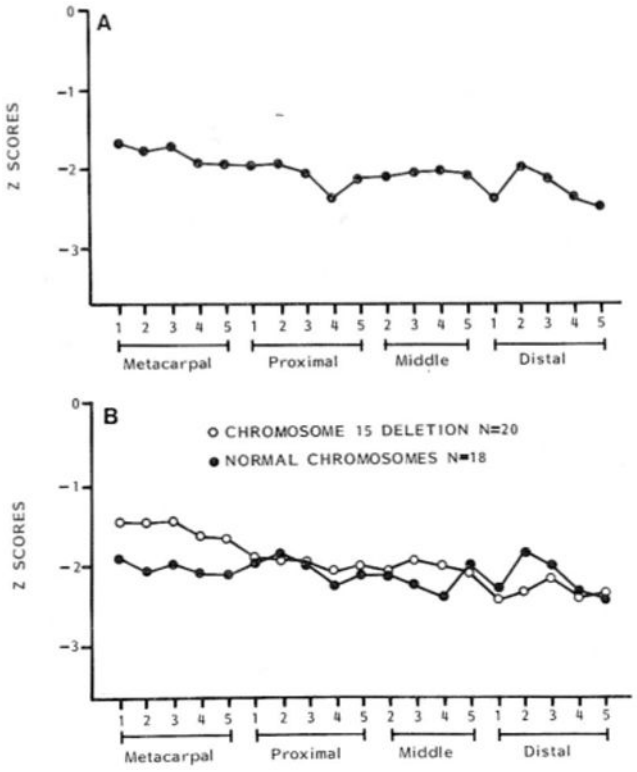

Fig. 1.

A. Mean metacarpophalangeal pattern profile produced from the individual hand profiles of 38 Prader-Labhart-Willi syndrome patients with and without the chromosome deletion. B. Mean metacarpophalangeal pattern profile for chromosome deletion (N = 20) and nondeletion (N = 18) Prader-Labhart-Willi syndrome individuals.

TABLE 1

Syndromes analyzed for metacarpophalangeal pattern profile

Syndrome	Reference
Achondroplasia	Landry et al. (1979), Poznanski (1984)
Acrodysostosis	Poznanski et al. (1977)
Apert	Poznanski (1984)
Asphyxiating thoracic dystrophy	Poznanski (1984)
Brachydactyly E	Poznanski et al. (1977)
Carpenter	Kaler et al. (1981)
Chotzen	Escobar and Bixler (1977)
Cleiodocranial dysplasia	Poznanski (1984)
Cockayne	Poznanski (1984)
Coffin-Siris	Hayes and Say (1977)
Cri-du-chat	Fenger and Niebuhr (1978)
Crouzon	Kaler et al. (1982)
De Lange	Peeters (1975), Halal and Preus (1979)
Diastrophic dwarfism	Poznanski (1984)
Down	Poznanski et al. (1972a)
Ellis-van Creveld	Poznanski (1984)
Familial hypoplastic thumb	Miura (1984)
Frontometaphyseal dysplasia	Poznanski (1984)
Hand-foot-uterus	Poznanski et al. (1972a), Giedion and Prader (1976)
HGH isolated deficiency	Poznanski (1984)
Holt-Oram	Poznanski et al. (1970, 1972a,b)
Hypochondroplasia	Poznanski (1984)
Hypophosphatasia	Poznanski (1984)
Juberg-Hayward	Poznanski (1984)
Klinefelter	Poznanski et al. (1977)
Kniest	Poznanski (1984)
Laron dwarfism	Poznanski (1984)
Larsen	Poznanski (1984)
Marfan	Poznanski (1984)
Metaphyseal chondrodysplasia (Schmid, McKusick and Jansen types)	Poznanski (1984)
Metatropic dwarfism	Poznanski (1984)
Monosomy 9p	Young et al. (1983)
Mucolipidosis II	Poznanski (1984)
Mucolipidosis III	Poznanski (1984)
Mucopolysaccharidosis I-H; I-H/S; I-S; II, IV, VI	Poznanski (1984), Arias and Zimmer (1979)
Multiple epiphyseal dysplasia	Poznanski (1984)
Myositis ossificans progressiva	Poznanski (1984)
Osteochondrodysplasia type Irapa	Arias et al. (1979)
Otopalatodigital	Gall et al. (1972), Poznanski et al. (1973)

Syndrome	Reference
Pfeiffer	Kaler et al. (1982)
Prader-Labhart-Willi	Butler et al. (1982), Butler and Meaney (1985)
Pseudoachondroplastic dysplasia	Poznanski (1984)
Pseudohypoparathyroidism (PHP/PPHP)	Poznanski et al. (1977), Mooij et al. (1985)
Robinow	Robinow and Chumlea (1982), Shprintzen et al. (1982)
Saldino-Mainzer	Poznanski (1984)
Seckel	Poznanski (1984)
Silver	Poznanski (1984)
Sotos	Halal (1982), Poznanski (1984), Butler et al. (1985)
Spondylometaphyseal dysplasia	Poznanski (1984)
Thalidomide embryopathy	Arias et al. (1980)
Thanatophoric dwarfism	Poznanski (1984)
Thrombocytopenia-absent-radius	Poznanski (1984)
Tricho-rhino-phalangeal-type 1	Poznanski et al. (1974), Felman and Frias (1977), Say et al. (1977), Dijkstra (1983)
Tricho-rhino-phalangeal-type 2	Dijkstra (1983)
Trisomy 9p	Schinzel (1979)
Turner	Poznanski et al. (1972a, 1977), Park (1977)
XXXY	Poznanski (1984)
XYY	Poznanski (1984)

TABLE 2

Discriminant analysis for MCPP Z score variables[1]

Variables in function	Discriminant loading	Discriminant coefficient
3rd proximal phalanx	−0.68	−1.16
2nd middle phalanx	−0.42	0.60
Age (years)	0.69	0.65

[1] Sotos syndrome (N = 16) vs. normal (N = 41).