Published in final edited form as:

Am J Med Genet. 1988 December ; 31(4): 767–773. doi:10.1002/ajmg.1320310406.

Metacarpophalangeal Pattern Profile Analysis in Fragile X Syndrome

Merlin G. Butler, **Mark Fletcher**, **David D. Gale**, **F. John Meaney**, **D. Ross McLeod**, **Joel Fagan**, and **Nancy J. Carpenter**

Division of Genetics, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee (M.G.B., M.F.); Eastern Kentucky University, Richmond, Kentucky (D.D.G.); Department of Medical Genetics, Indiana University School of Medicine and Genetic Diseases Section, Indiana State Board of Health, Indianapolis (F.J.M.); Alberta Children's Hospital Research Center, Calgary, Alberta, Canada (D.R.M., J.F.); Chapman Research Institute of Medical Genetics, Children's Medical Center, Tulsa, Oklahoma (N.J.C.)

Abstract

We analyzed the metacarpophalangeal pattern profile (MCPP) on 18 male individuals from 16 families with fragile X—fra (X), or Martin-Bell—syndrome and calculated a mean syndrome profile. Fourteen of 18 individuals with fra (X) syndrome had significant positive correlations which indicated clinical homogeneity. Discriminant analysis of individuals with fra (X) syndrome compared with a sample of normal individuals produced a correct classification rate of 88% based on a function of 3 MCPP variables that may provide a useful tool in screening individuals for the fra (X) syndrome. Discriminant and correlation analyses of individuals with Sotos sequence and individuals with fra (X) syndrome did not identify MCPP similarities. Therefore, there was no MCPP evidence in our study of patients with Sotos sequence and fra (X) chromosome expression.

Keywords

Sotos sequence; metacarpophalangeal pattern profile (MCPP); pattern variability index; discriminant analysis; correlation studies; Martin-Bell syndrome

INTRODUCTION

The fragile X—fra (X) or Martin-Bell—syndrome is a well-recognized condition of mental retardation, macroorchidism, large or prominent ears, a long narrow face, hyperflexibility, and a characteristic chromosome fragile site at Xq27.3. The incidence of the fragile X syndrome is approximately one in 1,000 males [Herbst and Miller, 1980; Turner et al., 1986; Webb et al., 1986]. Due to phenotypic variability, early recognition of fra (X) individuals is difficult. Therefore, quantitative methods based on radiographic measurements may be helpful for identifying individuals for fra (X) chromosome studies.

Address reprint request to Merlin G. Butler, M.D., Ph.D., Division of Genetics, Department of Pediatrics, Vanderbilt University School of Medicine, T-2404 Medical Center North, Nashville, TN 37232.

Edited by John M. Opitz and James F. Reynolds

Metacarpophalangeal pattern profile (MCPP) analysis is an evaluation of the hand skeleton based on a comparison of the 19 tubular bone lengths to normal bone-length standards, as described by Poznanski et al. [1972] and Garn el al. [1972], This method provides a quantitative assessment of the amount and direction of abnormality of the hand skeleton. MCPP analysis has been used to evaluate numerous syndromes [Poznanski, 1984; Butler et al., 1986].

Recently, we applied a method of MCPP analysis on 18 fra (X) individuals to evaluate its potential as a screening tool to identify individuals for fra (X) chromosome studies.

MATERIALS AND METHODS

MCPP-Data

Posterio-anterior hand radiographs were obtained on 18 individuals diagnosed with fra (X) syndrome (Fig. 1). The group included 18 males from 16 families ranging in age from 2 to 40 years, with a mean age of 13 years. The average fra (X) chromosome expression was 13 *%* with a range from 1*%* to 35 %. Those males with low expression (<4%) had either a positive family history (e.g. affected brother) or had repeated cytogenetic studies that were positive.

Because patients with fra (X) chromosome expression and the Sotos sequence have been described [Beemer et al., 1986], MCPP data analysis was undertaken on 34 previously reported individuals with Sotos sequence (25 males and 9 females ranging in age from 0.8 to 24 years with a mean age of 5.9 years) [Butler et al., 1988] and our fra (X) syndrome patients in order to identify hand pattern differences and similarities between the 2 conditions. Results of fra (X) chromosome studies were normal on several of our Sotos sequence patients.

The metacarpophalangeal bone lengths of each patient were measured in millimeters with a vernier caliper and compared to bone-length standards (appropriate for age and sex) published by Gara et al. [1972], (white Americans, age 2 years to adulthood) and Poznanski [1974], (Gefferth Hungarian sample, birth to 15 months). Through these comparisons, Z score values for the 19 bones of each patient were obtained (Z score = observed bone length minus mean bone length divided by SD). Therefore, MCPP on a given patient is a set of 19 Z scores, which may be plotted on a graph or subjected to various statistical procedures for study and comparison with MCPP of other patients, or groups of patients [Poznanski et al., 1972]. Pattern variability index [$\Sigma Z^2/N - (\Sigma Z/N)^2$] for quantitation of hand changes as described by Garn et al. [1987] was also calculated from the MCPP data of our patients.

Correlation Studies

We derived a mean pattern profile from the 18 patients based on the average Z score for each bone [Poznanski et al., 1972; Garn et al., 1972]. The pattern from each patient was compared to this group mean pattern and to each other using Pearsonian correlation coefficients. Correlation studies comparing individuals with either fra (X) syndrome or Sotos sequence and between percent fra (X) expression and degree of similarity to the pattern profile mean were also undertaken.

Discriminant Analysis

A forward stepwise method of discriminant analysis [Enslein et al., 1977] was performed on the 19 Z score variables and age of individuals from 3 groups: the 18 patients with fra (X) syndrome, 34 patients with Sotos sequence and a control group of 41 normal individuals whose hand radiographs were randomly obtained from the records of Indiana University School of Dentistry. The 41 normal individuals included 17 males and 24 females, with an age range of 9 6/12 to 18 years and a mean age of 13 1/12 years.

RESULTS

The mean Z scores of the 18 patients with fra (X) syndrome fell between 0 and −1.5. Therefore, each measured hand bone was not significantly shorter than the mean of normal individuals. The mean pattern profile based on the 18 patients with fra (X) syndrome was fairly flat with one valley (fifth metacarpal —see Fig. 2).

Next, the correlation program was used to assess similarity between the mean pattern and each of the 18 individual patterns. Fourteen of 18 individuals had significant positive correlations (Table 1). There was not a significant correlation ($P<0.05$) between the percent fra (X) expression and degree of similarity to the pattern profile mean.

Discriminant analysis of the normal and fra (X) syndrome patients resulted in a discriminant function based on 3 of the 19 MCPP variables. In the discriminant analysis, patients with fra (X) syndrome were distinguished from normal individuals at an overall correct classification rate of 88% in this sample (Fig. 3). The 3 MCPP variables in the discriminant function were the Z scores representing the fifth metacarpal (X5); the second metacarpal (X2); and the fourth metacarpal (X4). Patients with fra (X) syndrome were also distinguished from Sotos sequence individuals at an overall correct classification rate of 88% based on one MCPP variable (fifth metacarpal) entered in the discriminant function.

Pattern variability index was calculated on each fra (X) syndrome patient and the average index was 0.16 with an average Z score of −0.48. This compared with an average pattern variability index of 0.31 with an average Z score of 2.86 for our 34 Sotos sequence individuals. A score below 0.70 is not considered abnormal [Garn et al., 1987].

Four recognized hand pattern profiles have been identified in Sotos sequence [Dijkstra, 1985; Wit et al., 1985; Butler et al., 1988]. Correlation studies to compare the mean hand pattern profile of fra (X) syndrome individuals with the 4 individual hand pattern profiles recognized in Sotos sequence individuals did not show significant similarities in the profiles of fra(X) syndrome or Sotos sequence individuals.

DISCUSSION

All the digits were within the normal range (+2 to −2 Z scores) in fra (X) syndrome patients. Although the metacarpals were consistently short, the shortest bone relative to normal values was the fifth metacarpal (average Z score equals −1.5). Our data indicating short metaearpals, particularly the 4th and 5th metacarpals, are in agreement with that reported by Carpenter et al. [1982]. The hand pattern profile was fairly flat with little up and down

deviation (excluding metacarpal area) as indicated by a low pattern variability index of 0.16. The correlations of the fra (X) syndrome individuals suggest a homogeneous pattern with 78% of the individuals possessing a significant correlation with the Z score group mean. Although the profile is fairly flat, a unique hand profile apparently exists for fra (X) syndrome based on these measurements and visual comparison with published profiles of other syndromes.

The results from our discriminant analysis suggest that effective delineation of fra (X) syndrome patients from normal individuals and from individuals with Sotos sequence with an 88% accuracy based on MCPP data. Additional testing with a larger sample size is needed to test the power of the discriminant method to distinguish patients with fra (X) syndrome not only from a normal sample but from patients with other conditions such as Sotos sequence.

The correlation and discriminant analyses of hand pattern profiles of Sotos sequence patients and fra (X) syndrome individuals did not indicate similarities. Therefore, our MCPP data do not support that Sotos sequence individuals have fra (X) chromosome expression. In summary, the observations presented in this report suggest the potential of MCPP analysis as a diagnostic tool in screening patients for the fra (X) syndrome.

Acknowledgments

The authors acknowledge the use of the facilities of Computing Services, University of Kentucky, Lexington and Eastern Kentucky University, Richmond. The authors wish to thank Margaret Lane, Sandy Cain, and Pam Phillips for their assistance.

References

Beemer FA, Veenema H, de Pater JM. Cerebral gigantism (Sotos syndrome) in two patients with fra(X) chromosomes. Am J Med Genet. 1986; 23:221–226. [PubMed: 3953650]

Butler MG, Dijkstra PF, Meaney FJ, Gale DD. Metacarpophalangeal pattern profile analysis in Sotos syndrome: A follow-up report on 34 subjects. Am J Med Genet. 1988; 29:143–147. [PubMed: 3344766]

Butler MG, Meaney FJ, Kaler SG. Metacarpophalangeal pattern profile analysis in clinical genetics: An applied anthropometric method. Am J Phys Anthropol. 1986; 70:195–201. [PubMed: 3740246]

Carpenter NJ, Leichtman LG, Say B. Fragile X-linked mental retardation. Am J Dis Child. 1982; 136:392–398. [PubMed: 7081157]

Dijkstra PF. Cerebral gigantism (Sotos syndrome). Metacarpophalangeal length in the evaluation of skeletal malformation. Radiology. 1985; 105:375–381.

Enslein, K., Ralston, A., Wilf, HS. Statistical Methods for Digital Computers. New York: John Wiley and Sons; 1977. p. 76-95.

Garn SM, Hertzog KP, Poznanski AK, Nagy JM. Metacarpophalangeal length in the evaluation of skeletal malformation. Radiology. 1972; 105:375–381. [PubMed: 5079664]

Garn SM, Leonard WR, Poznanski AK. Applications of the pattern variability index (OZ) to the quantification of dysmorphogenesis in the hand. Am J Med Genet. 1987; 27:143–152. [PubMed: 3605192]

Herbst DS, Miller JR. Nonspecific X-linked mental retardation II: The frequency in British Columbia. Am J Med Genet. 1980; 7:461–469. [PubMed: 7211956]

Poznanski, AK. The Hand in Radiological Diagnosis. 1st. Philadelphia: W.B. Saunders; 1974.

Poznanski, AK. The Hand in Radiological Diagnosis. 2nd. Philadelphia: W.B. Saunders; 1984.

Poznanski AK, Garn SM, Nagy JM, Gall JC. Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. Radiology. 1972; 104:1–11. [PubMed: 4260738]

Turner G, Opitz JM, Brown WT, Davies KE, Jacobs PA, Jenkins EC, Mikkelsen M, Partington MW, Sutherland GR. Conference report: Second international workshop on the fragile X and on X-linked mental retardation. Am J Med Genet. 1986; 23:11–67.

Webb TP, Bundey SE, Thake AI, Todd J. Population incidence and segregation ratios in the Martin-Bell syndrome. Am J Med Genet. 1986; 23:573–580. [PubMed: 3953667]

Wit JM, Beemer FA, Barth PG, Orthuys JWE, Dijkstra PF, van denBrande JL, Leschot NJ. Cerebral gigantism (Sotos syndrome). Compiled data of 22 cases. Analysis of clinical features, growth and plasma somatomedin. Eur J Pediatr. 1985; 144:131–140. [PubMed: 4043122]

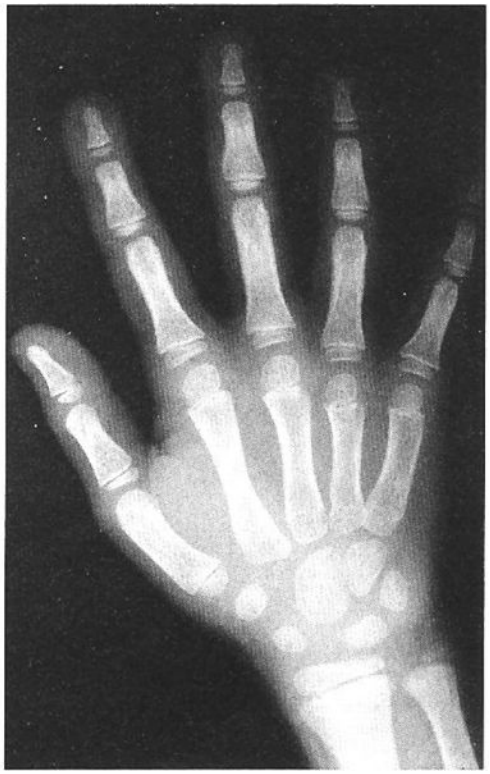

Fig. 1.
A typical hand radiograph from a 7-year-old-malc with the fra (X) syndrome.

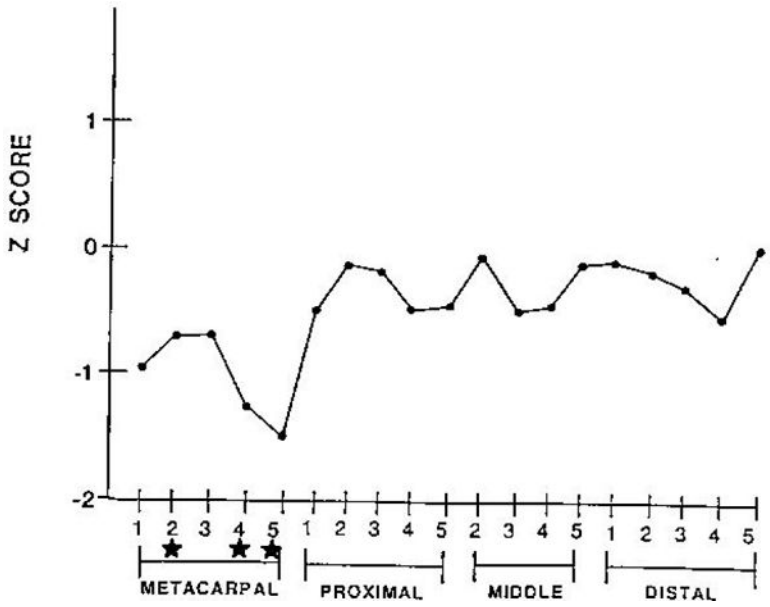

Fig. 2.

Mean MCPP for 18 individuals with fra (X) syndrome. (O) indicates the bones that were selected in the discriminant analysis.

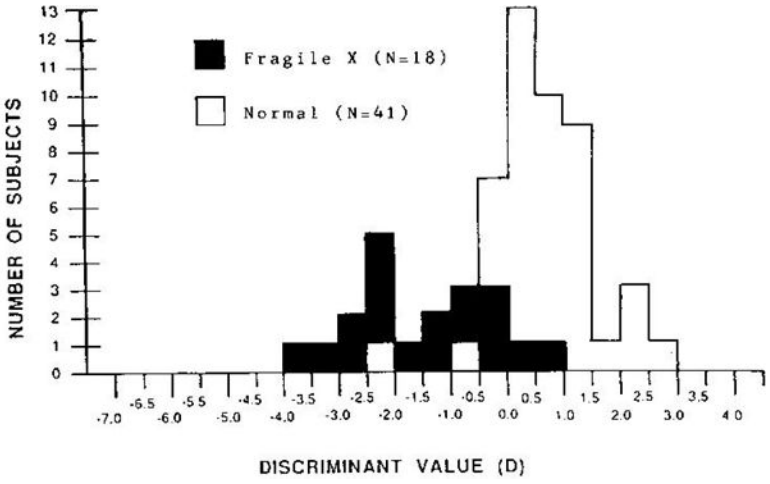

Fig. 3.

Histogram depicting normal and fra (X) syndrome classification by discriminant analysis. D = 0.28−2.19 (X2) + 1.25 (X4) + 1.20 (X5).

TABLE I

Correlations Between Individual and Group Mean MCPP in Fra (X) Syndrome

Age (years)	Sex	Fra (X) Expression (%)	Correlation
2.0	M	14	0.67**
2.0	M	6	0.52*
4.0	M	3	0.70**
5.0	M	3	0.35
5.0	M	12	0.76**
5.0	M	6	0.50*
6.0	M	8	0.67**
6.0	M	28	0.39*
7.0	M	4	0.40*
7.5	M	20	0.60**
8.0	M	15	0.26
10.0	M	35	0.36
16.0	M	21	−0.01
21.0	M	30	0.48*
28.0	M	5	0.67**
30.0	M	7	0.44*
31.0	M	20	0.52*
40.0	M	1	0.64**

*$P < 0.05$ for one-tailed test.

**$P < 0.005$ for one-taiied test.