Published in final edited form as:

Am J Med Genet. 1993 September 15; 47(4): 471–474. doi:10.1002/ajmg.1320470407.

Metacarpophalangeal Pattern Profile Analysis in Williams Syndrome

Michele A. Burns,

University of Calgary Medical School, Calgary, Alberta, Canada

D. Ross McLeod,

Alberta Children's Hospital Research Center, Calgary, Alberta, Canada

L. R. Linton,

Department of Biological Sciences, University of Calgary, Calgary, Alberta, Canada

Merlin G. Butler

Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee

Abstract

Many patients with Williams syndrome (WS) are not diagnosed until they are old enough to demonstrate the characteristic personality and facial changes. A number of these changes are quite subtle and none of them is present in all affected individuals. The cause of WS remains obscure and consequently, there are no cytogenetic, biochemical, or molecular studies to help in the diagnosis of patients in whom the diagnosis is uncertain. We have generated a mean WS metacarpophalangeal pattern profile (MCP) on 21 clinically diagnosed individuals with WS. This mean syndrome profile shows that WS hands are smaller than average age-matched control hands and that the distal phalanx of the thumb is disproportionately large with respect to the rest of the hand. A mathematical model, which effectively discriminates WS patients from unaffected control individuals, was developed using discriminant analysis of the MCP data. Of the 21 WS patients classified by this method, only 2 were misclassified as "normal." Similarly, 2 of the 24 control individuals were misclassified as "WS," yielding an overall successful classification rate of 91%.

Keywords

Williams syndrome; metacarpophalangeal pattern profile (MCP); computer-automated metacarpophalangeal profile system (CAMPS); discriminant analysis

INTRODUCTION

In 1961, Williams et al. described a disorder of supra-aortic stenosis, mental retardation, and unusual facial appearance. This same disorder was described independently by Beuren et al. [1962] who added dental anomalies and peripheral pulmonary artery stenosis as component manifestations. In 1963, Black and Carter recognized that the "elfin

facies” in children with idiopathic infantile hypercalcemia (IIH), was actually the same as in those described earlier by Williams et al. and Beuren et al. Williams syndrome (WS) is recognized as a sporadic genetic condition with a frequency of approximately 1:25,000 live births. The underlying cause for this multisystem disorder is unknown.

The typical WS face is present at birth but becomes more obvious with age [Jones and Smith, 1975]. The minor anomalies include flattening of the malar areas with full cheeks and lips, long philtrum, anteverted nares, depressed nasal bridge, pointed chin, and a wide mouth, which is frequently open. The eyes are often blue and many patients have a stellate pattern of the iris. There are often epicanthic folds, ocular hypertelorism, periorbital fullness, strabismus, and a medial eyebrow flare [Jones and Smith, 1975; Burn, 1986]. Although these children are often quite attractive as youngsters, the facial appearance tends to “coarsen” with age.

Approximately 75% of WS patients have a heart anomaly, most commonly supraventricular aortic stenosis and/or peripheral pulmonary artery stenosis [Burn, 1986]. Less frequent heart defects include ventricular septal defect, patent ductus arteriosus, hypertension, mitral valve prolapse, and bicuspid aortic valve [Morris et al., 1988; Hallidie-Smith and Karas, 1988].

The hallmark of WS is the characteristic and unusual personality seen in most patients. The children are very friendly, even with total strangers, and they have been described to have a “cocktail party” manner. Udwin and Martin [1987] found that compared with normal controls children, WS children tended to have an overly friendly manner in conversation and to use many clichés and “adult-type vocabulary.” The WS children’s verbal skills contrasted sharply with their much poorer perceptual and motor skills. Most WS patients are considered mildly to moderately mentally retarded with a mean IQ of 56 [Burn, 1986]. There has been some suggestion that IQ may steadily decrease with age, with adolescent WS patients progressing to moderate or severe retardation [Pagon et al., 1987].

When hypercalcemia occurs in the WS patients, these individuals may also suffer from failure to thrive, vomiting, constipation, diarrhea, and nephrocalcinosis, especially as infants. In many patients the hypercalcemia is only transient; however, in some patients, it may persist beyond infancy and lead to skeletal changes in adolescence and adulthood as well as a variety of dental anomalies [Burn, 1986].

Broadening the definition of WS to include patients without detectable cardiac anomalies or hypercalcemia has led to making the diagnosis of WS in a great many more children. However, in many such children, the clinical findings are quite subtle and many parents have had to settle with a diagnosis of possible WS. Further strain for the parents is the fact that patients with WS are diagnosed at a mean age of 4 years and 3 months [Udwin, 1990]. Thus, many families must struggle for a number of years until a diagnosis is finally made.

The first attempt to quantify the diagnosis of WS was the Preus index [Preus, 1984]. This method evaluated the presence of 50 characteristics, gave them a numerical score, and compared them with the distribution for WS patients. Preus claimed that this index could successfully diagnose 99% of all patients capable of being evaluated. However, its actual

usefulness has been limited, by the very subjective nature of classifying subtle physical traits.

MCPP analysis involves measuring the tubular lengths of the 19 bones of the hand and comparing these lengths to normal bone length standards. This technique was first described by Garn et al. [1972], who collected data on over 600 individuals to determine the standard lengths of the hand bones. This method has been used to quantify the amount and type of abnormality in the hand skeleton [Poznanski, 1984]. Such analysis has been used successfully in the evaluation of many genetic syndromes including Prader-Willi syndrome [Butler et al., 1982] and Fragile X syndrome [Butler et al., 1988]. In both examples, mean pattern profiles were generated, to which individual patient profiles were then correlated.

We have applied this method of analysis to 21 individuals with clinically confirmed WS to evaluate its ability to discriminate WS patients from unaffected controls.

MATERIALS AND METHODS

Radiographic Analysis and MCPP Analysis

Radiographs from right and/or left hands were obtained on 21 individuals with WS. All diagnoses were made by dysmorphologists. We were unable to obtain radiographs of both hands on all patients, as most investigators prefer to evaluate only the left hand. Table I summarizes relevant patient information as well as some of our pattern profile data.

The patients ranged in age from 15 months to 25 years. We measured the total length of each of the 19 bones in each hand, including the epiphyses, if present. Rather than manual measurement with vernier calipers, the bone lengths were measured with the computer-automated metacarpophalangeal profile system (CAMPS) described by Coupland et al. [1985]. This program measures the bone lengths, stores the data on disk, and then compares the measurements to age and sex-matched normative data originally described by Poznanski et al. [1972]. These data are then converted to *Z*-scores and displayed graphically.

In order to give equal weight to each patient in the final analysis, it was necessary to combine the *Z*-scores on those patients with radiographs for both hands. Thus, the *Z*-score for each bone measurement of one hand was added to the *Z*-score for the corresponding bone on the opposite hand and the average bone length for the two hands was used in the analysis.

One collaborator provided us with actual bone measurements rather than sending radiographs and it was necessary to calculate the *Z*-scores for these patients manually, using Poznanski's tables of normal data [1972].

Statistical Methods

Discriminant analysis was used to develop discriminant functions for "normal" individuals and WS patients (MGLH module in SYSTAT Version 5.01). Stepwise linear regression was used to obtain an initial subset of the 19 variables to examine. Variables were then added to or removed from this subset until the Wilks' Lambda statistic was minimized and all

variables in the model were significant. These data were used to generate the two discriminant functions shown in Table II.

RESULTS

Figure 1 represents the mean MCPD on the 21 individuals with WS. All the mean Z -score values fell between -0.66 and -2.01 . The normal range for Z -scores is ± 2.0 , therefore all the WS patients' hand bone measurements fell within the normal range, albeit consistently on the small side. The peak on the graph corresponds to the distal phalanx of the thumb, which indicates that this bone is relatively larger than the other hand bones. The other 4 distal phalanges are actually quite small when compared with the rest of the hand.

A correlation matrix was generated, which compared each patient's MCPD to the mean MCPD as well as to the other 20 patients. The entire matrix is not shown; however, the correlation between each patient and the mean MCPD is included in Table I.

The two diagnostic discriminant functions obtained are detailed in Table II. To use these functions to discriminate between WS and normal patients, measurements of the 7 indicated bones (ME5, P3, P4, M4, D1, D3, and D5) are made and converted to Z -scores. It is important that the standard lengths and standard deviations of these lengths presented by Poznanski [1972] be used for the transformation. Each discriminant function is then solved using the Z -transformed bone lengths. Thus, for each test case, the lengths of the 7 indicated hand bones are measured and converted to Z -scores. These values are then used in both of the equations given in Table II. The equation that gives the larger result corresponds to the predicted condition.

The results of using these functions to classify the individuals in the original data set are given in Table III. Nineteen of the 21 WS individuals were correctly classified as were 22 of the 24 normal individuals, for an overall correct classification rate of 91%.

DISCUSSION

Patients with WS have been found to have a fairly distinctive MCPD when their hands are compared to those of unaffected individuals. The distal phalanges are the most striking, with the distal phalanx of the thumb (D1) appearing to be disproportionately large compared to the rest of the hand. The remaining distal phalanges seem to taper in size until D5 which is not only small with respect to the rest of the hand in WS, but is also the only bone which falls outside of the normal range altogether (± 2.0).

Our goal was to develop a reasonably objective method of discriminating WS patients from unaffected individuals. To date, the Preus index [Preus, 1984] has been the only diagnostic tool available when patients without hypercalcemia or a cardiac anomaly are suspected to have WS. However, this index is cumbersome and relies on very subjective interpretation of subtle clinical manifestations.

The results from the present study suggest that our method of using MCPD analysis to generate mean Z -scores and then applying diagnostic discriminant functions is capable of

differentiating between WS patients and unaffected controls in 91% of our WS and control cases and should provide a novel and objective method of diagnosing WS in suspected cases.

As our patients ranged in age from infants to adults, this method can be successfully applied to test cases of all ages. The major advantage is its use in the very young patient with WS, which may then potentially alleviate much of the frustration previously experienced by parents whose children remained undiagnosed for many years.

REFERENCES

- Beuren AJ, Schulze C, Eberle P, Harmjanz D, Apitz J (1962): The syndrome of supraaortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance. *Am J Cardiol* 13:471–482.
- Black JA, Carter REB (1963): Association between aortic stenosis and facies of severe infantile hypercalcemia. *Lancet* 2:745–748. [PubMed: 14055045]
- Burn J (1986): Williams syndrome. *J Med Genet* 23:389–395. [PubMed: 3537294]
- Butler MG, Kaler SG, Yu P-L, Meany FJ (1982): Metacarpophalangeal pattern profile analysis in Prader-Willi syndrome. *Clin Genet* 22:315–320. [PubMed: 7160103]
- Butler MG, Fletcher M, Gale DD, Meany FJ, McLeod DR, Fagen J, Carpenter NJ (1988): Metacarpophalangeal pattern profile analysis in Fragile X syndrome. *Am J Med Genet* 31:767–773. [PubMed: 3239565]
- Coupland SG, McLeod DR, Wesenberg RL, Lowry RB (1985): CAMPS: Computer-automated metacarpophalangeal profile system. *Am J Med Genet* 22:375–381. [PubMed: 3840331]
- Garn SM, Hertzog KP, Poznanski AK, Nagy JM (1972): Metacarpophalangeal length in the evaluation of skeletal malformation. *Radiology* 105:375–381. [PubMed: 5079664]
- Hallidie-Smith KA, Karas S (1988): Cardiac anomalies in Williams-Beuren syndrome. *Arch Dis Child* 63:809–813. [PubMed: 3415298]
- Jones KL, Smith DW (1975): The Williams elfin facies syndrome. *J Pediatrics* 86:718–723.
- Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL (1988): Natural history of Williams syndrome: Physical characteristics. *J Pediatr* 113:318–326. [PubMed: 2456379]
- Pagon RA, Bennett FC, LaVeck B, Stewart KB, Johnson J (1987): Williams syndrome: Features in late childhood and adolescence. *Pediatrics* 80:85–91. [PubMed: 3601523]
- Poznanski AK (1984): “The Hand in Radiologic Diagnosis,” 2nd ed. Philadelphia: W.B. Saunders.
- Poznanski AK, Gam SM, Nagy JM, Gall JC Jr (1972): Metacarpophalangeal pattern profiles in the evaluation of skeletal malformation. *Radiology* 104:1–11. [PubMed: 4260738]
- Preus M (1984): The Williams syndrome—objective definition and diagnosis. *Clin Genet* 25:422–428. [PubMed: 6723102]
- Udwin O (1990): A survey of adults with Williams syndrome and idiopathic infantile hypercalcemia. *Dev Med Child Neurol* 32:129–141. [PubMed: 2338177]
- Udwin O, Martin N (1987): Cognitive abilities and behavioural characteristics of children with idiopathic infantile hypercalcemia. *J Child Psychol Psychiat* 28:297–309. [PubMed: 3584299]
- Williams JCP, Barratt-Boyes BG, Lowe JB (1961): Supraaortic stenosis. *Circulation* 24:1311–1318. [PubMed: 14007182]

Fig. 1.
Mean MCP on the 21 individuals with WS.

TABLE I.

Patient Information and Pattern Profile Data

Sex	Age (years)	Hand used	Correlation coefficient
M	2	RH/LH	0.45 ^a
M	4	RH/LH	0.54 ^a
F	6	RH/LH	0.65 ^a
F	9	RH/LH	0.13
M	12	RH/LH	0.47 ^a
F	25	RH/LH	0.23
F	3	LH	0.37
M	4	LH	0.69 ^a
F	4	LH	0.29
F	4	LH	0.32
M	4	LH	0.35
F	7	RH	0.69 ^a
M	11	LH	0.49 ^a
M	15	LH	0.12
M	5	RH/LH	0.50 ^a
M	4	RH/LH	0.54 ^a
M	12	RH/LH	-0.38
M	21	RH/LH	0.06
F	2	RH/LH	0.63 ^a
M	2	LH	0.15
F	3	RH/LH	0.04

^aSignificant.

TABLE II.

Diagnostic and Discriminant Functions for WS and Normal Individuals

	WS	Normal
Constant	-3.573	-0.968
ME5	0.212	-0.630
P3	1.919	0.484
P4	-2.414	-0.364
M4	1.278	-0.321
D1	0.711	-0.251
D3	-2.828	-0.083
D5	-1.356	0.623
Equation I (WS): $-3.573 + (ME5 \times 0.212) + (P3 \times 1.919) + (P4 \times -2.414) + (M4 \times 1.278) + (D1 \times 0.711) + (D3 \times -2.828) + (D5 \times -1.356)$		
Equation II (Normal): $-0.968 + (ME5 \times -0.630) + (P3 \times 0.484) + (P4 \times -0.364) + (M4 \times -0.321) + (D1 \times -0.251) + (D3 \times -0.083) + (D5 \times 0.623)$		

TABLE III.

Observed Versus Expected Results After Using the Discriminant Functions to Classify all Individuals

Observed	Predicted	
	WS	Normal
WS	19	2
Normal	2	22