CONGENITAL MALFORMATIONS
THE INFLUENCE OF GENETIC AND NONGENETIC FACTORS

Progress Report

Charles M. Woolf
Arizona State University
Tempe, Arizona
85281

January 1, 1973 - December 31, 1973

PREPARED FOR THE U. S. ATOMIC ENERGY COMMISSION UNDER
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ABSTRACT

During the years 1961-1966 and 1969-1973, research has been carried out at Arizona State University to determine the importance of genetic and nongenetic factors for specific congenital malformations in man. This work has been supported by the U. S. Atomic Energy Commission. Before the etiological role of mutation can be evaluated for congenital malformations, it is necessary to obtain this information. During the present contract period (1973), data have been collected on (1) the incidence of congenital hip disease in the San Carlos Apache Indians, (2) the sex ratio of individuals with Type I syndactyly and (3) the frequency of spontaneous abortions and stillbirths in control families for spina bifida cystica. During the grant period, one manuscript was published; another manuscript was written for publication. A manuscript on a genetic study of syndactyly in Utah is in press.

INTRODUCTION

A research program has been carried out in the Department of Zoology, Arizona State University, Tempe, Arizona during the periods 1961-1966 and 1969-1973, to evaluate the importance of genetic and non-genetic factors for specific congenital malformations in man. This work has been supported in its entirety by the U. S. Atomic Energy Commission.

During the first eight months (January 1, 1973 - August 31, 1973) of the present contract period, the primary activities were to (1) continue studies on congenital hip disease in the Apache Indians of Arizona, (2) search the world literature for pedigrees of Type I Syndactyly and analyze sex ratio data of individuals showing this anomaly, (3) continue studies on spina bifida cystica, and (4) write a manuscript on the dermatoglyphic patterns in children with specific congenital malformations.

During this period the principal investigator spent in excess of the contracted 10% of the academic year period working on the project. During the remainder of the current term (September - December) the co-principal investigator will devote in excess of 10% of the academic year period to the project.

CONGENITAL HIP IN THE APACHE INDIANS

Etiologic heterogeneity exists for congenital hip disease (acetabular dysplasia and hip subluxation, or dislocation). Both genetic and nongenetic factors influence the probability that this anomaly will occur. Carter and Wilkinson (1964) proposed that congenital hip disease (symbolized by CHD) has at least two genetic components. They proposed that the depth of the joint socket is determined by polygenes, and generalized joint laxity is probably due to a dominant gene. Woolf (1971) concluded that genetic factors play an important etiological role, but a definitive statement could not be made as to the nature of the genetic mechanism. Nongenetic factors which are known to influence the risk of CHD include season of birth, order of birth, and breech malposition at birth. These exogenous factors seem to play a more important role in females than males in determining whether CHD will occur; hence, this disorder is more heritable in males than females.

The incidence of CHD varies among populations. High incidence values have been reported for Navajo and Apache Indian populations living in Arizona. A prevalence rate of 38/1000 was reported by Rabin et. al. (1965) for the Navajo Indians living at Many Farms, Arizona. Kraus and Schwartzmann (1957) observed a minimum incidence of 30.5/1000 among the Fort Apache Indians living at Whiteriver, Arizona. Both the Navajo and Apache Indians are members of the Athabascan linguistic stock.

There are two Apache Indian populations in Arizona: the White River population (n = 6000) and the San Carlos population (n = 4500). Preliminary

investigations have indicated that the incidence of CHD is much higher among the Fort Apache Indians than the San Carlos Indians. An investigation has been initiated to explore this suggestion. Specific aims of this study are (1) to determine the incidence of CHD in these two Apache Indian populations; (2) to do a genetic analysis of CHD in these populations; (3) to estimate the coefficient of inbreeding in these two populations; and (4) to investigate the importance of certain nongenetic factors such as birth order, breech malposition and season of birth.

Two incidence values for CHD have been obtained for the San Carlos Indian population. Names of all Apache Indian children born between January, 1960 and December, 1972 were obtained from the fifth revision of the 1970 census record. This record attempts to assess the lineage of each individual in the population. It was possible, therefore, to exclude children who were mixtures of San Carlos Apache and some other tribe (or race) from the study. The medical record of each full-blood child was reviewed at the Public Health Service hospital in San Carlos. Complete medical histories were recorded for children affected with CHD. A total of 1108 medical records were surveyed. Eight children (all females) were noted to have either provisional, probable, or confirmed congenital hip dislocation or dysplasia. This procedure leads to an incidence value of 7.22/1000 in the San Carlos population.

A second incidence value was obtained by using a hospital list of births occurring between January, 1963 and January, 1970. This list records the

names of children born at the hospital or those born at home and brought into the hospital shortly after birth. There is no distinction between full and mixed blood children on this list; all children on the list were included in the study. The medical record of each child was reviewed. Of the 1128 children whose medical records were surveyed, six (all females) were diagnosed as having provisional, probable or confirmed congenital hip dislocation or dysplasia. This gives a prevalence value of 5.32/1000.

Figures that are derived from similar ascertainment methods are needed for the White River Apache population. The incidence value for the Fort Apache population reported by Kraus and Schwartzmann (1956) represents minimum prevalence. The authors estimate that not more than 50 per cent of the total cases had been located, and cases of dysplasia and subluxation were not included in the study. Because of a delay in obtaining approval from the Fort Apache Tribal Council, it has not yet been possible to obtain incidence data for the White River Apache population. U. S. Public Health Hospital authorities have requested that this research should be carried out during the winter months when the demands on their medical records are minimal by outside research teams. Accordingly, work requiring medical records at White River has been postponed until the autumn of 1973.

It seems apparent, however, that a difference in prevalence values between the San Carlos and White River Apache populations does exist.

Epidemiologic and inbreeding studies will be carried out in the coming year to gain insight into the reasons for this difference. It is proposed that a study of congenital hip disease among the Apache Indians will be the major research project of the next contemplated contract period, as measured by funds and time expended.

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THE PROBLEM OF SEX RATIO IN CASES OF SYNDACTYLY TYPE I

Because of the dominant mode of inheritance of many types and the conspicuous nature of digital anomalies, syndactyly is a prime congenital malformation for family history studies. A genetic study of syndactyly in Utah has been made by the Principal Investigator (Woolf, in press). Propositi were selected from medical records in hospitals in the larger cities of Utah (Salt Lake City, Ogden, and Provo). Large kindreds were encountered with Type I Syndactyly (Zygodactyly) and Type II Syndactyly (Synpolydactyly). Of interest is the strong sex ratio favoring males which occurs in the Utah kindreds with members showing Type I syndactyly. The reasons for this distorted sex ratio remain enigmatic. Two different hypotheses present themselves: (1) The aberrant sex ratio results from lower penetrance in females than males; (2) The aberrant sex ratio results from segregation distortion in males involving the Y chromosome and the autosome which carries the dominant mutant gene. In order to test these hypotheses an attempt was made to obtain a large number of pedigrees. Thirty five pedigrees of Syndactyly Type I were located by searching the world literature. Sixteen were added from the study of syndactyly in Utah. The 51 pedigrees have been divided into two sub-groups: Syndactyly Type Ia includes kindreds in which affected members have webbing only between the second and third toes. Syndactyly Type Ib includes kindreds in which affected members have webbing between the third and fourth fingers and/or the second and third toes with occasional involvement of other digits.

The data from 26 pedigrees of Syndactyly Type Ia are presented in Table 1. In these pedigrees there are 175 affected individuals; 109 are males (62%) and 66 are females (38%). The data do not support the hypothesis that the aberrant sex ratio is due to lower penetrance in females than males. Such a hypothesis would predict that "skips" in pedigrees would occur more frequently in females than males. In the 26 pedigrees under study, nine heterozygous individuals who were free of the trait transmitted the dominant gene to one or more offspring. Eight were males; one was a female.

In the pedigrees, affected fathers produced 187 offspring, of which 104 (55.6%) were affected. This value does not deviate significantly from the expected Mendelian value of 50% ($\chi^2 = 2.14$, $.2 > P > .1$). Yet, 77.4% of the sons and 34.8% of the daughters were affected. Each of these two values do differ significantly from the expected Mendelian value of 50% ($\chi^2 = 26.9$, $\chi^2 = 7.9$, respectively). Such a severe distortion of frequency values is not observed among the progeny of affected females. A total of 63 offspring were produced by these females. Of this number, 27 (42.9%) had Syndactyly Ia. This frequency value does not deviate significantly from the expected Mendelian value of 50% ($\chi^2 = 1.0$, $.5 > P > .3$). However, 53.1% of their sons were affected and only 32.3% of their daughters were affected. Neither of these frequency values deviates significantly from 50% ($\chi^2 = .03$, $.9 > P > .8$; $\chi^2 = 3.2$, $.1 > P > .05$, respectively). Since the sex ratio of progeny (95 sons: 92 daughters) of affected fathers is normal, a type of differential sperm dysfunction seems to be ruled out where the favored

sperm is one with the Y chromosome and the dominant gene for syndactyly. However, the data are compatible with the hypothesis of segregation distortion where at the first meiotic division, the dominant gene tends to go to the same pole as the Y chromosome. Tending to negate this hypothesis, however, is the troublesome low frequency value of affected daughters (32.3%) of affected mothers. Even though this value does not deviate significantly from 50%, it is nevertheless of the same magnitude as the frequency of daughters (34.8%) of affected fathers. It is possible that this low frequency value is merely an example of sampling error; however, it may also manifest some other phenomenon.

Analyses of published pedigrees can often lead to erroneous conclusions. Pedigrees that appear in the literature may have been submitted for publication solely because they show many affected individuals. Furthermore, there may be a tendency to omit normal sibs from such pedigrees. Accordingly, in these pedigrees, the frequency of affected offspring produced by affected parents may tend to be high. It is apparent that more kindreds of Syndactyly Type Ia are needed before a definitive statement can be made about the inheritance of this anomaly.

The distorted data for Syndactyly Type Ia become even more meaningful when a comparison is made with the data for Syndactyly Type Ib. The data for the latter anomaly, resulting from an analysis of 25 pedigrees, are given in Table 2. There are 195 affected members of these pedigrees; 90 (46%) are females and 105 (54%) are males. The sex ratio data fit a

1:1 ratio ($\chi^2 = 1.01$; $.5 > P > .3$). All data are compatible with the hypothesis of autosomal dominant inheritance with reduced penetrance in females and males. In these pedigrees there were 27 skips; 15 of these were females and 12 were males. There is no significant difference in the frequency of affected sons of affected fathers and the frequency of affected sons of affected mothers. The high proportion of affected sons of fathers heterozygous for Syndactyly Type Ia is not observed in the sons of fathers heterozygous for Syndactyly Type Ib.

TABLE 1

Offspring of parents heterozygous for Syndactyly Type Ia

Parentage	Sex	Total	Normal	Affected	"Skipped"	Percent Affected	Transmission Frequency*
Heterozygous Fathers	Sons	95	18	72	3	77.42	80.65
	Daughters	92	59	32	1	34.78	35.87
	Total	187	77	104	4	55.61	57.75
Heterozygous Mothers	Sons	32	14	17	1	53.13	56.25
	Daughters	31	21	10	0	32.26	32.26
	Total	63	35	27	1	42.86	44.44

* Transmission Frequency: Frequency of heterozygotes in the offspring of heterozygotes

TABLE 2

Offspring of parents heterozygous for Syndactyly Type Ib

Parentage	Sex	Total	Normal	Affected	"Skipped"	Percent Affected	Transmission Frequency*
Heterozygous Fathers	Sons	111	56	49	4	44.55	48.18
	Daughters	93	51	37	4	40.22	44.57
	Total	204	107	86	8	42.16	46.08
Heterozygous Mothers	Sons	108	59	40	8	37.04	44.44
	Daughters	111	65	35	11	31.53	41.44
	Total	219	124	75	19	34.25	42.92

* Transmission Frequency: Frequency of heterozygotes in the offspring of heterozygotes

A GENETIC STUDY OF SPINA BIFIDA CYSTICA

Controversy exists in the medical literature concerning the etiologic importance of genetics for spina bifida cystica (meningocele and myelomeningocele). In order to gain insight into this problem, a genetic study was carried out in Utah. Family histories were obtained for 107 probands with either meningocele or myelomeningocele. The frequencies of this disorder and other congenital malformations were obtained in the following group of relatives of the probands: sibs, parents, grandparents, aunts, uncles and first cousins. It soon became evident that it was difficult to obtain accurate data on spina bifida cystica in relatives other than sibs. For that reason all analyses were limited to sibs and other pregnancies of the mother of the probands.

Although other studies appearing in the medical literature suggest that the frequency of sibs with spina bifida cystica and other malformations of the central nervous system is of the order of 3% to 7%, the frequency value obtained in this study was much lower. The probands had 314 sibs (live births). Only 2 (.64%) of these sibs were born with spina bifida cystica. This value suggests that in Utah, spina bifida cystica is characterized by a low familial aggregation of cases.

Since malformations of the central nervous system frequently lead to stillbirths or spontaneous abortions, a study was designed to compare the frequency of these types of abnormal pregnancies in the mothers of the probands with controls. Although a set of controls will be obtained from Utah, one set, readily available, was obtained from medical records

at St. Joseph's Hospital in Phoenix, Arizona. These records were utilized because of the large number of Catholics who attend this hospital. Mormons and Catholics are characterized by large families. Obstetrical records are available in St. Joseph's Hospital that are notable because of the completeness of pregnancy histories. Control females were matched with the mothers of the propositi with spina bifida cystica on the basis of total number of live births. That is, if the mother of a propositus had 6 live births (including the propositus), the first female encountered in the obstetrical records with 6 live births was used as the control. An exact match was not possible in one case. A mother of a propositus who had 12 live births was matched with a female having 11 live births because a control female having 12 live births could not be located.

The pregnancy histories of the mothers of the propositi and control females are presented in Tables 1 and 2. There are no significant differences in the frequencies of fetal deaths between the two groups; 13.2% of the pregnancies of the mothers of propositi ended in spontaneous abortion, which is very similar in magnitude to the frequency (13.1%) of miscarriages in the control females ($\chi^2 = .003$, $.975 > P > .9$). Stillbirths occurred at frequencies of 2.6% and 1.02% in the pregnancies of mothers of propositi and control females, respectively. This difference is also not statistically significant ($\chi^2 = 3.443$, $.1 > P > .05$).

If spina bifida cystica has a polygenic mode of inheritance with a threshold liability, where the responsible genes may also cause anencephaly, the prediction would be an increase in the frequency of stillbirths and mis-

carriages in the other pregnancies of the mothers of the propositi as compared with the controls. Such an increase is not evident in these data. The results of this study do not support the hypothesis that spina bifida cystica has a strong genetic basis. Unknown nongenetic factors seem to play an important etiologic role for this congenital malformation.

TABLE 1

PREGNANCIES OF MOTHERS OF PROPOSITI WITH SPINA BIFIDA

LIVE BIRTHS				
Sex	Total	----- Affected with -----		
		Spina Bifida	Multiple Congenital Malformations	Hydrocephalus
Sibs:				
Males	143	2	1	0
Females	170	0	1	0
Unknown Sex	1	0	0	1
Sum	314	2	2	1
Propositi:				
Males	45	(45)		
Females	62	(62)		
Sum	107	(107)		

TOTAL NUMBER OF LIVE BIRTHS (Sibs + Propositi) = 421				

FETAL DEATHS			
Sex	Total	Stillbirths	Miscarriages
Sibs:			
Males	6	6	
Females	2	2	
Unknown Sex	71	5	66
Sum	79	13	66
% of Total Pregnancies	15.8%	2.6%	13.2%
TOTAL NUMBER OF FETAL DEATHS = 79			

TOTAL NUMBER OF PREGNANCIES (Live Births + Fetal Deaths) = 500

TABLE 2

PREGNANCIES OF CONTROL FEMALES

LIVE BIRTHS				
Sex	Total	Affected with		
		Spina Bifida	Multiple Congenital Malformations	Anencephalus
Males	226	0	1	1
Females	187	0	0	0
Unknown Sex	7	0	0	0
Sum	420	0	1	1
TOTAL NUMBER OF LIVE BIRTHS = 420				

FETAL DEATHS			
Sex	Total	Stillbirths	Miscarriages
Males	2	2	
Females	0	0	
Unknown Sex	67	3	64
Sum	69	5	64
% of Total Pregnancies	14.1%	1.02%	13.1%
TOTAL NUMBER OF FETAL DEATHS = 69			

TOTAL NUMBER OF PREGNANCIES (Live Births + Fetal Deaths) = 489

A STUDY OF DERMATOGLYPHIC ASYMMETRY IN CHILDREN WITH FIVE DIFFERENT CONGENITAL MALFORMATIONS

Man is a bilaterally-symmetrical organism; each half of the organism tends to develop as a mirror-image of the other. The developing organism attempts to do the same thing simultaneously in each half but may fail to a greater or lesser degree. These deviations from perfect symmetry may be directional and occur consistently in the species, such as the difference in thickness of the ventricles of the mammalian heart or they may be fluctuating and occur randomly. Results of a number of investigations suggest that certain types of environmental and genetic stress can lead to increases in fluctuating asymmetry (Tebb and Thoday, 1954; Mather, 1953; Waddington, 1960; Van Valen, 1962; Bader, 1965; Adams and Niswander, 1967; Bailit, 1970 and Sofaer, 1971). An increase in fluctuating asymmetry indicates a decrease in developmental buffering or the ability to resist developmental accidents.

Adams and Niswander demonstrated that children with familial cleft lip $\pm$ cleft palate have an increased asymmetry of their dermatoglyphics and molar teeth. The objective of the present investigation is to further test the hypothesis that increased fluctuating asymmetry is an indicator of abnormal growth, by studying the dermatoglyphics of children with five different congenital malformations: (1) cleft lip $\pm$ cleft palate, (2) club foot (talipes equinovarus), (3) congenital dislocation of the hip, (4) spina bifida cystica and (5) cleft palate (without cleft lip).

Materials and Methods

A total of 638 individuals made up the study group for this investigation. This includes 331 children with congenital defects and 307 children who served as controls. Table 1 shows the entire group classified according to deformity, race and sex. Patients with isolated cleft palate and patients with Pierre-Robin syndrome were grouped separately from those with cleft lip & cleft palate because many studies indicate they are separate genetic entities (Fraser, 1961; Carter, 1969; Woolf, 1971; Carroll, 1971). The club foot patients all had talipes equinovarus and the spina bifida cystica cases had either meningocele or myelomeningocele. All patients were obtained at Barrows Neurological Center of St. Joseph's Hospital or The Crippled Children's Hospital in Phoenix, Arizona. The control group was obtained from schools, head start programs and from patients admitted to the hospitals for reasons other than congenital defects. An attempt was made to match the controls and patients for sex, age and race.

Permanent dermal prints were obtained on all individuals using the Faurot inkless method (Walker, 1957) and the technique of Aase (1971). The palm prints were analyzed following the classification of Penrose (1968). Infants under one year were not included in the study because of the difficulty in obtaining clear prints on infants. The dermatoglyphic features studied included the following:

- 1) Axial triradial position: The position of the most distal axial triradius was calculated using the method of Penrose (1949) known as the

maximal atd angle. This angle was obtained by drawing a line from the a and d triradii to the t triradius (see Fig. 1). The angle thus formed was measured by protractor and recorded in degrees. This gave a quantitative measurement by means of which the differences between the two hands could be computed. The mean and the variance for left and right hands were computed for the various groups as well as the intra-pair variance between hands of a single individual. Absolute values were used in this calculation (L-R). The intra-pair variance or the variance between hands of an individual has been identified as a measure of fluctuating asymmetry (Reeve, 1960, Waddington, 1960; Van Valen, 1962; Adams and Niswander, 1967). The F value was computed by dividing the intra-pair variance for the patients by the intra-pair variance for the controls (Table 2).

2) Finger patterns: The patterns on the fingertips were recorded as arches, tented arches, radial loops, ulnar loops, whorls, central pocket loops, double loops and accidentals. Each paired structure (e. g. right thumb and left thumb) was examined for pattern asymmetry. The score for the fingers of one individual could range from zero (no fingers alike) to five (all five pair show symmetry). The Mann-Whitney U Test was used to compare the central tendency of the scores of the patients and controls. The corrected z values are shown in Table 3.

3) Main-line index: The main lines A, B, C and D are the proximal radiants of the triradii a, b, c and d found at the base of the four fingers (see Fig. 1). They are an indication of the generalized ridge direction over

the palm. The general direction can be determined from the two main lines A and D and is called the main-line index. The classification of the main lines is based on a numbered sequence of positions around the periphery of the palm. Each main-line is described by the position at which it terminates. Cummins' (1939) main-line index was used for scoring. The scores for the A-line could range from one to six and the scores for the D-line could range from one to eight. The difference between a main-line score on the right hand and the main-line score on the left hand was taken as the measurement of the amount of asymmetry between hands of an affected individual. The Mann-Whitney U Test was used to compare these differences for the patients and the controls.

Results and Discussion:

1) Position of the axial triradius: The results summarized in Table 2 show that significant differences were found in the intra-pair variance (the variance between the hands of each individual) which has been identified as a measure of fluctuating asymmetry. All groups with congenital defects showed significant increases in fluctuating asymmetry when compared with their control group.

The atd angle was the most sensitive feature studied. This is not too surprising as the atd angle is determined by the position of the axial triradius and this in turn is thought to be dependent on the differentiation of the first digit to become a functional (opposable) thumb, which is an

evolutionary landmark in man. No axial triradius is present when the thumb is missing (Holt, 1968).

2) Finger patterns: The Mann-Whitney U Test was used to analyze the finger patterns as explained previously. The corrected z values are recorded in Table 3. Ten groups were found to have increased asymmetry for finger patterns when compared with the controls.

3) Main-line index: The Mann-Whitney U Test was used to analyze the A-line and the D-line separately. The corrected z values are recorded in Table 3. The main-lines are an index of the transverseness of the dermal ridges. The course of the A-line and the palmar configurations in the proximal portion of the palm would be dependent on one another and it would seem plausible to find a positive correlation between the position of the axial triradius and the course of the A-line. Significant differences were found in twelve of the thirteen groups studied.

The D-line was found to show significant differences in six of the thirteen groups. Some racial tendencies were noted; i.e. none of the Indian groups were found to have increased asymmetry between D-lines. The Caucasian groups showed the most asymmetry but seemed to depend also on the defect involved, as the Caucasian spina bifida group did not show increased asymmetry nor did the Pierre-Robin group which was 60% Caucasian.

The results of this investigation appear to conform to the hypothesis that increased fluctuating asymmetry can be regarded as a criterion of

abnormal growth which in turn is related to the degree of canalization of the individual, making the individual insensitive to the potentially disturbing effects of environmental stresses and minor variations of its genotype.

Summary:

The objectives of the present investigation were to test the hypothesis that increased fluctuating asymmetry is an indicator of abnormal growth and to determine if dermatoglyphics or dermal ridges are sensitive indicators of the level of developmental stability.

Four malformations (cleft lip $\pm$ cleft palate, club foot, congenital dislocated hip and spina bifida cystica) were chosen for the study which appear to have a polygenic mode of inheritance with a threshold beyond which individuals are at risk. Patients with isolated cleft palate or the Pierre-Robin syndrome were grouped separately from the cleft lip (p) based on the many studies indicating they are separate entities. Four palmar dermatoglyphic features were analyzed to determine the level of fluctuating asymmetry. All groups with congenital deformities showed increased levels of fluctuating asymmetry when compared with control groups. Some features analyzed were more sensitive indicators than others. The atd angle was the most sensitive feature studied followed by the A-line and finger patterns.

The results indicate that the canalizing ability of these children has been lowered with the resulting increase in the frequency of developmental

accidents and the increase in fluctuating asymmetry of their palmar dermatoglyphics. The positive correlation between fluctuating asymmetries of unrelated characters in the same individual indicates a general buffering capacity and this in turn suggests that the level of fluctuating asymmetry can be used to measure developmental stability of individuals and populations. It is also concluded that palmar dermatoglyphics are sensitive to adverse genetic and environmental conditions and therefore are good criteria of morphological stability.

Figure 1

Table 1

The study group classified according to deformity, race and sex

Group	Total No. in Group	Males	Females	Caucasian		Mexican		Indian	
				M	F	M	F	M	F
Cleft lip (P)	103	65	38	32	22	23	8	10	8
Club foot	65	41	24	27	19	13	5	1	0
Congenital hip	70	15	55	4	17	2	5	9	33
Spina bifida	61	32	29	14	17	13	9	3	5
Cleft palate	23	8	15	5	7	2	7	0	1
Pierre-Robin	10	4	6	3	3	1	3	0	0
Controls	307	165	142	80	67	51	35	34	40

Table 2

Analysis of the std angle with groups classified according to deformity and race
Measurement is in degrees

	(n)	Left Hand		Right Hand		Intra Pair
		Mean	Variance	Mean	Variance	Variance
Cauc. cleft lip (P)	50	49.26	97.83	48.48	118.74	74.38 **
Mex. cleft lip (P)	31	49.81	74.63	50.81	98.69	67.00 **
Ind. cleft lip (P)	18	47.28	15.86	48.00	40.94	36.21 **
Cauc. club foot	43	47.12	42.01	45.51	49.87	35.05 **
Mex. club foot	18	52.67	80.00	53.72	94.09	75.23 **
Cauc. cong hip	16	46.12	46.65	47.75	50.73	42.92 **
Mex. cong hip	7	49.71	87.57	51.71	78.90	114.67 **
Ind. cong hip	41	44.10	23.79	43.00	28.10	28.79 **
Cauc. spina bifida	26	48.69	86.30	48.31	114.78	139.61 **
Mex. spina bifida	17	51.12	106.11	49.53	106.76	152.51 **
Ind. spina bifida	9	51.44	115.53	52.89	178.61	52.03 **
Cleft palate	23	46.04	52.23	46.04	56.86	42.09 **
Pierre-Robin	10	48.00	114.67	46.40	65.38	208.49 **
Cauc. controls	147	43.63	59.04	43.78	60.12	5.22
Mex. controls	86	45.87	40.61	45.51	38.94	14.66
Ind. controls	74	44.20	20.71	44.11	27.11	5.79

* Significant F value

** Highly significant F value

Table 3

Analysis of finger patterns, D-line exits and A-line exits
for asymmetry using the Mann-Whitney U Test
The corrected z values are recorded

Group	Finger patterns	D-line exits	A-line exits
Caucasian cleft lip (P)	3.652 **	1.979 *	3.243 **
Mexican cleft lip (P)	2.968 **	1.609	3.565 **
Indian cleft lip (P)	2.363 **	1.034	2.199 *
Caucasian club foot	3.162 **	3.240 **	4.334 **
Mexican club foot	2.122 *	0.771	3.664 **
Caucasian cong. hip	2.923 **	3.571 **	3.387 **
Mexican cong. hip	1.552	1.131	2.552 **
Indian cong. hip	4.620 **	0.952	3.669 **
Caucasian spina bifida	1.494	1.279	4.001 **
Mexican spina bifida	3.122 **	1.985 *	4.273 **
Indian spina bifida	1.877 *	1.005	3.531 **
Cleft palate (isolated)	2.341 **	2.406 **	3.231 **
Pierre-Robin syndrome	0.437	0.543	0.536

* Significant z value

** Highly significant z value

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