Amer J Hum Genet 25:405–412, 1973

Polydactyly: A Genetic Study in South America

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INTRODUCTION

Polydactyly has been recognized as a hereditary trait in man since ancient times, not only in the Old World [1] but also in pre-Columbian America (fig. 1). Nevertheless, many fundamental facts about the genetics of polydactyly remain unsolved primarily because of etiological heterogeneity, which is not taken into consideration when large-scale studies based on hospital or health records are performed.

Although polydactyly is known to be about 10 times more frequent in Negroes than Caucasians [2–3] as a result of a differential frequency for the postaxial type [4], this still is a heterogeneous entity which requires further definition, as clearly stated by Woolf and Woolf in 1970 [5]. Data on incidence, ethnic correlation, penetrance, and expressivity for each recognized polydactyly type obtained through the Latin American Collaborative Study for Congenital Malformations [6] are presented here.

MATERIALS AND METHODS

In the 54-month period from July 1967 to December 1971, there were 185,704 consecutive live births examined at 47 maternity hospitals located in three adjoining countries: Uruguay, Chile, and Argentina. Eight defined geographic areas were considered: (1) Montevideo, Uruguay; (2) Santiago, Chile; (3) Buenos Aires city metropolitan area, Argentina; (4) Pampas, Argentina; (5) Central Argentina; (6) Cuyo, Argentina; (7) northeastern Argentina; and (8) Comahue, Argentina.

Each live birth was examined by a pediatrician trained by members of the medical genetics center to assure consistent reliable information. A special record was kept for each detected malformed baby as well as for the like-sexed nonmalformed live birth immediately following in time of occurrence within each hospital. Thus, a 1:1 paired control group by sex, place, and time of birth was obtained. Both major and minor malformations were described in detail by the pediatrician in each case.

Polydactyly was diagnosed in 214 live births but 26 cases were excluded because of polysyndactyly or other associated malformations. Thus, 188 cases with polydactyly as the single diagnosed malformation were considered for this study. These were defined and classified after Temtamy and McKusick [7] into six different types: preaxial 1 = thumb and/or big toe polydactyly; preaxial 2 = polydactyly of a triphalangeal thumb; preaxial 3 = polydactyly of the index finger; postaxial A = polydactyly of a well-formed articulated extra digit at the ulnar or fibular edge; postaxial B = polydactyly of an incomplete

Received December 11, 1972; revised February 28, 1973.

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FIG. 1.—Two of the three footprint-petroglyphs with postaxial polydactyly, probably of the pedunculated postminimi type, found by the authors at Talampaya, La Rioja, Argentina, a ceremonial valley from Aguada Culture, A.D. 1000. From their length : breadth ratio, the left print appears to be from a child, while the right print, as well as the third one not shown here, from an adult.

unarticulated nonfunctional extra digit at the ulnar or fibular edge. A sixth type, postaxial M (mixed), has been added to include cases in which both A and B types are present at different limbs in the same individual.

Family data obtained by special inquiry from the mother included parental ages and consanguinity, sibship composition, and malformations in relatives. Pedigree records at least through third-degree relatives were prepared whenever consanguinity or malformations in the family were detected.

Ethnic extraction information was collected since January 1970 by asking the mother whether the baby had one or more ancestors within each of the following eight categories: Latin Europeans, non-Latin Europeans, Jews, natives, Arabians, Negroes, Orientals, and other. Ethnicity [8] rather than race was, therefore, considered here.

To obtain an indicator for Negro participation in ethnic admixture at each studied area, the available data from 3,202 consecutive malformed and control live births were pooled after determining homogeneity between the groups (malformed group, 33/1,601; control group, 26/1,601; $\chi^2 = 0.844$; $P < .40$).

RESULTS

Frequency

Polydactyly, as a single malformation, was detected in 1.01 per 1,000 examined live births.

By type and sex (*table 1*). The observed relative distribution for the 168 cases of specified types was 18.5% for all preaxial (16.1% for type 1, 1.8% for type 2, and 0.6% for type 3); and 81.5% for all postaxial (14.3% for type A, 59.5% for type B, 2.3% for type M, and 5.4% for postaxial not further specified).

TABLE 1

POLYDACTYLY TYPE AND SEX

SEX	PREAXIAL			POSTAXIAL				NFS	TOTAL
	1	2	3	A	B	M	NFS		
Male	20	2	0	15	54	1	5	9	106
Female	7	1	1	9	46	3	4	11	82
Total	27	3	1	24	100	4	9	20	188
Sex ratio ...	2.86	2.00	0.00	1.67	1.17	0.33	1.25	0.82	1.29

NOTE.—NFS = not further specified.

A higher frequency of affected males was detected for preaxial-1 polydactyly, since the observed sex distribution was significantly different from the expected 1:1 ratio ($\chi^2 = 6.130$; $P < .025$).

There were four cases of mixed A and B postaxial polydactyly: a male with type A on left foot and B on both hands; a female with type B on left hand and A on the other three limbs; a female with type A on right and B on left foot; and a female with type A on right and B on left hand.

By geographic area (*table 2*). There is homogeneity for incidence of polydactyly for areas 2–8 (0.082%, $\chi^2 = 3.456$, df = 6, $P < .80$). Area 1 shows a significantly higher value (0.172%, $\chi^2 = 12.429$, $P < .0005$). When each polydactyly type is considered, only the postaxial-B type substantiated the higher incidence of area 1 (0.091%) relative to the other areas (0.049%) ($\chi^2 = 6.281$, $P < .025$).

When the frequency of preaxial-1 polydactyly is compared in two major areas, namely west (areas 2, 6 and 8) and east (the rest), the frequency was higher in the west (0.025%) than in the east (0.009%) ($\chi^2 = 7.623$, $P < .01$).

TABLE 2

POLYDACTYLY TYPE AND GEOGRAPHIC AREA

AREA	EXAMINED LIVE BIRTHS	PREAXIAL			POSTAXIAL				NFS	TOTAL	
		1	2	3	A	B	M	NFS		*N*	%
1	22,085	4	1	0	4	20	0	5	4	38	0.172
2	24,129	6	0	0	4	10	0	1	1	22	0.091
3	77,029	7	1	1	10	33	4	2	8	66	0.086
4	5,330	0	0	0	0	3	0	0	0	3	0.056
5	13,314	0	0	0	1	8	0	0	3	12	0.090
6	32,892	8	1	0	4	21	0	1	3	38	0.116
7	4,621	0	0	0	1	2	0	0	0	3	0.065
8	6,304	2	0	0	0	3	0	0	1	6	0.095
Total	185,704	27	3	1	24	100	4	9	20	188	0.101

NOTE.—NFS = not further specified.

By ethnic extraction. One or more Negro ancestors were recognized in 45 of 350 (12.85%) live births in area 1, compared with 14 of 2,852 (0.49%) for the other areas ($\chi^2 = 261.115$, $P < .0005$). No significant differences were detected for Oriental ancestors between the above-defined west and east areas.

Expressivity

The following three criteria were used for expressivity analysis (see table 3).

Affected region (upper or lower limbs). Hands were preferentially affected in

TABLE 3

EXPRESSIVITY AND FAMILIAL RECURRENCE

	PREAXIAL			POSTAXIAL					
POLYDACTYLY TYPE	1	2	3	A	B	M	NFS	NFS	TOTAL
Region:									
Upper	24(2)	3(1)	1	2(2)	79(38)	1(1)	3(1)	5(1)	118(46)
Lower	2	0	0	16(4)	9(2)	1	5(1)	6(3)	39(10)
Both	0	0	0	6(2)	11(2)	2(1)	1	6(3)	26(8)
Side:									
Left	10	1	1	6(1)	44(17)	0	4(1)	6(2)	72(21)
Right	12(2)	0	0	8(1)	14(6)	0	1	2(1)	37(10)
Both	5	2(1)	0	10(6)	39(19)	4(2)	3(1)	5(4)	68(33)
No. affected limbs:									
1	22(2)	1	1	12(2)	60(23)	0	6(1)	8(4)	110(32)
2	5	2(1)	0	8(4)	30(17)	2(1)	2(1)	5(1)	54(25)
3	0	0	0	1	4	1	0	2(1)	8(1)
4	0	0	0	3(2)	5(2)	1(1)	1	2(1)	12(6)
Total familial cases	2	1	0	8	42	2	2	7	64

NOTE.—Numbers within parentheses represent familial cases. NFS = not further specified.

preaxial-1 ($\chi^2 = 18.614$, $P < .0005$) and postaxial-B ($\chi^2 = 44.544$, $P < .0005$) types. Inversely, feet were mainly affected in the postaxial-A type ($\chi^2 = 6.532$, $P < .025$).

Affected side (left or right). Left hands were mainly affected in postaxial-B ($\chi^2 = 6.616$, $P < .025$). For all other polydactyly types, both sides were affected equally.

Number of affected limbs. Only one or two limbs were simultaneously affected in the preaxial types while from one to all four were affected in the postaxial types.

Genealogies

Pedigree data were available for 176 polydactyly propositi. Recurrence of polydactyly in other family members was detected in 64 (36.4%) cases (table 3). This finding could reflect larger family size.

Parental consanguinity was seen in four cases. One was a sporadic postaxial A

produced by sib parents (incest). Two sporadic postaxial-B types were products of first-cousin marriages. The fourth case, with first-cousin parents, was a postaxial polydactyly of unspecified type with other affected members in his family. Only one case of first-cousin consanguinity was observed in the parents of the control group (1/172).

Parental Ages

Paternal and maternal ages at the birth of the propositus was analyzed for both sporadic and familial cases of the postaxial-B type. The mean paternal and maternal ages, respectively, were 29.0 (SD = 7.67) and 25.4 (SD = 6.81) years for 50 sporadic cases and 27.1 (SD = 7.88) and 23.2 (SD = 5.86) years for 40 familial cases. These average values do not differ significantly.

Penetrance

Recurrence percentages were obtained for parents and sibs of the propositus as well as for sibs of the affected parent from eight postaxial-A and 42 postaxial-B familial cases (table 4). Since no significant differences were seen among those

TABLE 4

POSTAXIAL POLYDACTYLY: PENETRANCE

	POSTAXIAL A				POSTAXIAL B			
RELATIVES	Parents	Sibs	APS	Total	Parents	Sibs	APS	Total
Unaffected:								
N	13	14	18	45	63	40	126	229
Affected:								
N	3	7	13	23	21	11	31	63
%	18.8	33.3	41.9	33.8	25.0	21.6	19.8	21.6
Total (*N*)	16	21	31	68	84	51	157	292

NOTE.—APS = affected parent's sibs.

recurrence percentages, they were pooled together. The observed values were higher for the postaxial-A (33.8%) than for the B (21.6%) type ($\chi^2 = 4.588$, $P < .05$). Under the hypothesis of autosomal dominant inheritance, penetrance was then estimated as 0.68 for the postaxial-A and 0.43 for the postaxial-B type. Since penetrance was studied in the same way in both groups, we could assume that the possible ascertainment error is minimized.

Gene Frequencies

These were estimated assuming autosomal dominant inheritance for all types of polydactyly with all affected individuals heterozygous for the gene. The following results were obtained: preaxial $1 = 7.5 \times 10^{-5}$; preaxial $2 = 8.0 \times 10^{-6}$; pre-

axial 3 = 2.6×10^{-6}; postaxial A = 1.3×10^{-5}; and postaxial B = 4.6×10^{-4} (area 1) and 2.5×10^{-4} (all other areas). These results were not corrected for incomplete penetrance.

Mutation Rates

These were estimated by the direct method: preaxial 1 = 6.5×10^{-5}; preaxial 2 = 5.3×10^{-6}; preaxial 3 = 2.6×10^{-6}; postaxial A = 3.2×10^{-5}; and postaxial B = 1.4×10^{-4}.

DISCUSSION

The observed overall incidence of polydactyly in this study (1.01 per 1,000) is comparable with other published data, provided differences in ascertainment are considered. The postaxial-B type, usually only represented by an insignificant skin tag, will frequently be omitted from hospital or health statistics, but included in special prospective newborn studies considering both major and minor malformations as here reported. Findings on postaxial types, representing 80% of all polydactyly, are therefore in agreement with other similar studies [4] while discordant with data obtained from surgical cases [5].

Preaxial-1 polydactyly. This form had a higher frequency of affected males and a low frequency of familial recurrence. Of the two familial cases observed, one had a pedigree compatible with autosomal dominant inheritance while the other had only a maternal aunt equally affected. These data suggest a complex etiological mechanism as previously suggested by Woolf and Woolf [5].

Only hands were affected in five cases with bilateral involvement as well as in the majority of unilateral cases (no side preference). There were two cases with only affected feet.

Preaxial-1 polydactyly is known to be the most frequent type among Chinese [4, 9]. Nevertheless, we could not detect a higher incidence of Oriental ancestors in those areas with a higher frequency of preaxial-1 type.

Preaxial-2 polydactyly. Only hands were affected in the three detected cases. The only familial case showed a pedigree suggestive of autosomal-dominant transmission with high penetrance.

Preaxial-3 polydactyly. The only observed case was sporadic.

Postaxial-A polydactyly. There was a similar incidence value for all covered geographic areas. Mainly feet were involved with no side preference. Familial cases showed high penetrance. The estimated mutation rate falls within known limits for other autosomal-dominant traits [10].

Postaxial-B polydactyly. This form accounted for more than half of all cases of polydactyly. There was a higher incidence in area 1 (Uruguay) where a higher frequency of Negro ancestors was observed. This leads to the assumption that the known higher incidence of polydactyly among Negroes is at least partially due to the postaxial-B type. Mainly hands were affected and preferentially the left limbs. This left-side preference has been reported for polydactyly in guinea pigs and chickens [11].

To evaluate any paternal age effect on mutation, the sample has to be increased since incomplete penetrance would obviously tend to dilute it. The two cases produced by consanguineous parents could represent either chance association or known recessive syndromes with polydactyly, which could be missed in the newborn period. The high estimated mutation rate suggests involvement of either multiple loci or other genetic mechanisms. This form remains a heterogeneous entity.

Postaxial-M $(A + B)$ *polydactyly.* This was observed in four babies born at three different hospitals within area 3. Coexistence of both types in the same individual is not likely to represent chance association of two independent mechanisms judging from the incidence of types A and B in area 1. Both A and B forms of postaxial polydactyly have been described within a single family [5–12]. The hypothesis that a gene responsible for the B type interacts with modifier genes to produce the A phenotype does not fit the data well. Two of the four detected cases in this study were familial, showing an autosomal-dominant pattern of inheritance. Unfortunately, no information is available about polydactyly type in their affected relatives.

The observed differences between A and B postaxial polydactyly types supports the hypothesis of independent etiologic mechanisms for each, involving at least two different loci and very likely more.

SUMMARY

Polydactyly was observed as the single diagnosed malformation in 188 of 185,704 (0.101%) consecutive live births examined at 47 hospitals in Argentina, Chile, and Uruguay. The observed incidence was significantly higher in Uruguay (0.172%) where there also was a higher frequency of Negro ancestors (12.85%). For the other geographic areas the incidence of polydactyly was 0.091% and that of Negro ancestors, 0.49%. Postaxial-B polydactyly was the type responsible for the observed differential frequency. There was a higher frequency of affected males for preaxial 1, which involved upper limbs more frequently than lower ones as did the postaxial-B type. The inverse was seen for postaxial A. Postaxial B preferentially affected the left side.

The estimated penetrance of postaxial polydactylies was 0.68 for type A and 0.43 for type B under an autosomal-dominant hypothesis. Gene frequencies and mutation rates were estimated under the same hypothesis; values were not corrected for incomplete penetrance.

The observed differences between A and B types of postaxial polydactylies suggest the involvement of different loci and the high estimated mutation rate for type B (1.4×10^{-4}) suggests genetic heterogeneity.

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