Possible Genetic Carriers in the Spherophakia-Brachymorphia Syndrome*

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INTRODUCTION

The spherophakia-brachymorphia syndrome was first recognized by Marchesani (1939) to be distinct from Marfan's syndrome. This syndrome is characterized by spherophakia, brachydactyly, microphakia, ectopia lentis, glaucoma and myopia; the present investigation has identified a large *atd* angle of the palmar dermatoglyphics (fig. 4) as an additional stigma.

Marchesani believed the severe form of the syndrome to depend upon homozygous genes and the less severe form to be single gene effects. In subsequent studies by other authors a dominant mode of inheritance was suggested in two families and the recessive mode of inheritance first postulated was supported in 8 families. Although short fingers and short stature have been observed frequently in parents and siblings of affected individuals few anthropometric data on non-affected relatives have been reported. Neel (1947) directed attention to the importance of detecting genetic carriers of inherited diseases. In no study of the recessive type of spherophakia-brachymorphia syndrome has an attempt been made to define precisely the possible characteristics of the heterozygous carrier as distinct from the homozygous normal and homozygous affected.

The purposes of the present study are: (1) to report certain anthropometric and ophthalmic observations made in 5 fully affected individuals and their relatives; (2) to suggest stigmata which may be useful in distinguishing heterozygous carriers from homozygous normals and homozygous affected. Pedigrees showing the relationships of all individuals in this study are given in figures 1 and 2. Original data are listed in tables 13 and 14.

HISTORY

The following review of literature is limited to the criteria found useful in selecting heterozygotes. "Normal" describes individuals who in the light of the present study may have been normal homozygotes or heterozygous carriers.

Among 8 cases of supposed Marfan's syndrome Weill (1932) recorded the case of a 42-year-old affected female who was 142 cm. tall and had "short swollen fingers with extremities permitting only imperfect opening and closing."

Marchesani (1939) reported a study of 2 families. In 1 family the syndrome occurred in an 8-year-old male with stature of 108 cm., shortened fingers and toes, and thick musculature. The normal father was 158 cm. tall and had short plump hands and fingers. The normal mother was 153 cm. tall and had small hands. Three

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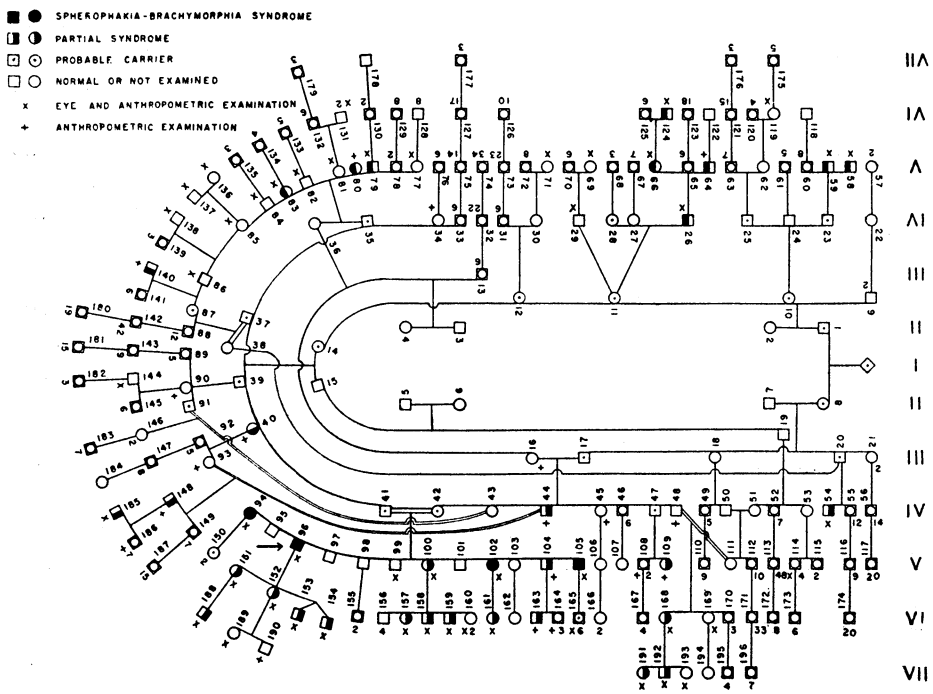

FIG. 1. Pedigree of Kindred 1 showing recessive type of spherophakia-brachymorphia in a family of French descent with partial syndrome caused by single gene. Reference numbers of individuals are above the symbols; numbers below the symbols are the numbers of individuals, if more than one, represented by a single symbol.

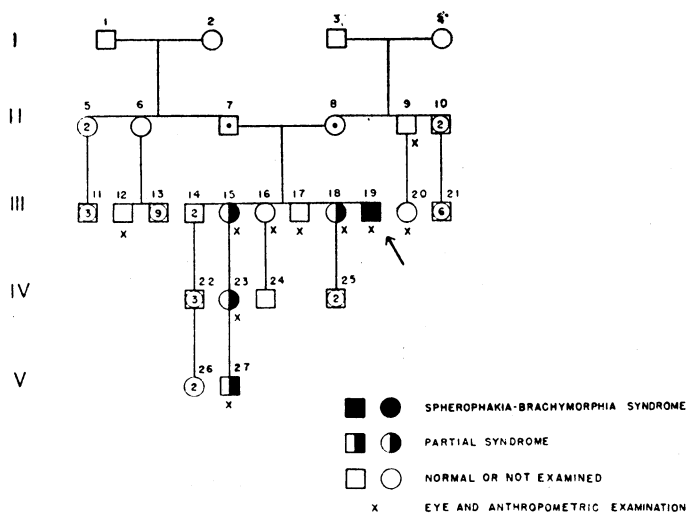

FIG. 2. Pedigree of Kindred 2 showing recessive type of spherophakia-brachymorphia in a family of Italian descent with partial syndrome caused by a single gene. Reference numbers of individuals are above the symbols; numbers within symbols are the numbers of individuals, if more than one, represented by a single symbol.

of the father's 6 living siblings were small and 3 were normal or large. Four siblings of the mother were normal. In Marchesani's second family a 36-year-old affected male whose stature was 147 cm. had relatively short hands and fingers. A 38-year-old affected brother was 156 cm. tall and had small hands. A 33-year-old affected sister with small hands was 153 cm. tall. A normal 38-year-old sister was 150 cm. tall and a normal 32-year-old brother was 152 cm. tall but had small hands. The deceased father was reported to be normal and 160 cm. tall. The 69-year-old normal mother was 150 cm. tall.

Meyer and Holstein (1941) observed 4 cases of spherophakia-brachymorphia and 2 normal siblings in a family whose parents were first cousins. A 17-year-old affected female was 138.4 cm. tall and had stubby hands, short fingers, short tibia, short feet and short toes. A 26-year-old affected sister was 141.0 cm. tall. A 23-year-old affected sister was 138.4 cm. tall and a 21-year-old affected brother was 144.8 cm. tall. The 2 normal brothers were of normal height. The statures of the father and mother were 163.8 and 148.6 cm., respectively. These authors accepted the mode of inhertance proposed by Marchesani.

Schmid (1946) recorded the occurrence of spherophakia-brachymorphia in a 17-year-old male who had a stature of 158 cm., diminished span, and had short hands and feet; his father and mother were 164 and 151 cm. tall.

Diethelm (1947) observed 2 cases in a family of 3 children whose parents were first cousins. Complete anthropometric observations were included in his study. A 30-year-old affected female had a stature of 161 cm., span 161.5 cm., hand length 17 cm., and hand width 7.5 cm. Digits I to V measured 60, 66, 74, 76 and 56 mm. The 25-year-old affected brother had a stature of 163 cm., small hands and "exaggerated" span. The normal 28-year-old sister had a stature of 165 cm., span of 173 cm., and bilateral myopia of −3.00. The 56-year-old father had a stature of 170 cm., span 179 cm., medium-sized hands with strong fingers. Legs were well formed. The 59-year-old mother had a stature of 162 cm., span 165, and wide but well formed hands. Right and left lenses of glasses were −6.75 and −11.00 sphere. A 59-year-old paternal uncle of affected had a stature of 169 cm. and presbyopia. A 57-year-old uncle had a stature of 172 cm., strong hands and legs, and bilateral myopia of −2.00. A recessive mode of inheritance for the full syndrome was considered certain.

Stadlin and Klein (1948) recorded the occurrence of spherophakia-brachymorphia in an 18-year-old girl whose parents were first cousins. The affected girl had a stature of 160 cm., span 160, hand length 17.5 cm., strong legs and feet, and a peculiar walk. A normal sister was 146 cm. tall and of brachymorphic type. The normal father had very short hands and feet. The mother was short and stocky. In accord with previous authors, Stadlin and Klein accepted the mode of inheritance proposed by Marchesani and they believed small height or "brachymorphia" was a characteristic of heterozygotes.

Rousseau (1949) reported 9 cases of spherophakia-brachymorphia covering 4 generations. The eye and anthropometric findings in this family did not appear to differ from those in families of the recessive type.

Seeleman (1949) observed a 3-year-old boy with stature of 79 cm., plump extremities, abnormal shortness of fingers and toes which could be flexed only slightly. The mother was 160 cm. tall.

Arjona (1952) reported 2 cases of spherophakia-brachymorphia in one family and one case in another. In one family the cousin parents had a 24-year-old affected daughter and a 29-year-old affected son who were both short and brachydactylous. No details were recorded about the 6 normal siblings and the parents. In another family, in which the parents were second cousins, Arjona observed a 16-year-old female with the syndrome. No anthropometric observations were reported in the patient, 4 normal brothers, or normal parents.

Probert (1953) found spherophakia-brachymorphia in a family but was uncertain about the mode of inheritance. A 42-year-old affected female had minimi that were shorter than normal. A 38-year-old brother had normal eyes but very short stature and short extremities. A 37-year-old affected sister had short fifth digits like her affected sister. A 26-year-old affected sister had brachyphalangy. A 24-year-old affected brother had shortened little fingers. The mother, a maternal uncle, a maternal aunt, and the maternal grandmother had brachyphalangy or brachydactyly. Four of the 7 children of the brachydactylous maternal uncle also had brachydactyly. No anthropometric observations were recorded for any members of the family and eye findings were limited to 5 of the 6 siblings.

Rosenthal and Kloepfer (1955) gave a full clinical report on eye findings and therapy of the 5 cases of spherophakia-brachymorphia included in the present study.

CRITERIA USED IN SELECTING HETEROZYGOTES

The criteria used to select heterozygotes were: (1) a related individual who possessed two or more stigmata of the syndrome, (2) the offspring or parent (assumed heterozygous) of a fully affected homozygote, or (3) the parent of a heterozygous child related to the propositus and possessing one or more stigmata of the syndrome. The 4 stigmata used in this study are believed to be the effects of a single gene; eye departures from normal in the direction of the syndrome, short stature, short fingers, and large *atd* angle.

Eye departures from normal in the direction of the syndrome were compound myopic astigmatism, myopic astigmatism, or simple myopia of more than 1 diopter. These deviations from normal were listed by Thorington (1944) to be expected in 8 percent, 1.5 percent and 1.5 percent, respectively, of the general population. A fraction of $\frac{1}{9}$ was used to calculate the expectation of encountering one of these slight departures in a person chosen at random.

Stature short enough to be expected approximately in $\frac{1}{20}$ or less in a random population was considered to be a second stigma of the syndrome. The means and standard deviations of stature based on American studies as listed by Watson and Lowrey (1951) were used as norms. Statistical tables which give the expectation of obtaining various deviations in a given direction from the mean were used to calculate the chance that the height of a relative would be a given distance below the norm. These calculations were later combined with those for other criteria to obtain the total chance occurrence of a particular partial syndrome on the assumption that the various stigmata are independent of one another.

Finger-palm index small enough to be expected approximately in $\frac{1}{7}$ or less of the control population was considered to be a third stigma of the syndrome. At the beginning of the investigation norms for means and standard deviations of finger-palm

index obtained from outline drawings were not available and an index of 73 or less was arbitrarily chosen in both sexes to indicate a deviation in the direction of the syndrome. After the heterozygous individuals were separated from the normal homozygous group, the finger-plam index values of the normal homozygotes were combined with index values of a non-related group to give a larger control group from which means and standard deviations were calculated separately for each sex. Using these values as norms, finger-palm index values small enough to be expected in 1/7 or less of the control population were considered to be deviations in the direction of the syndrome.

A sum of *atd* angles of the right and left hands large enough to be expected approximately 1/9 or less in a random population was considered to be a deviation in the direction of the syndrome and a fourth stigma. The means and standard deviations of *atd* angles as listed by Penrose (1954) were used as norms and his directions were followed to determine the size of the *atd* angles.

In a manner similar to that described for short stature the chance of obtaining finger-palm index values as small or smaller and the chance of obtaining *atd* angles as large or larger were determined for each person. When values for all 4 criteria were available the product of the 4 separate probabilities of obtaining each combination of stigmata, including a value of 1 or 1/9 for eye stigmata and counting a value of 1 for each stigma known to be absent, ranged from 4.2×10^{-3} to 5.8×10^{-10} in the group believed to be heterozygous; corresponding values ranged from 1 to 4.0×10^{-8} in the group believed to be homozygous normal. Probabilities of encountering an individual in the general population with stigmata deviating as much as or more in the direction of the syndrome were recorded in tables 10 and 11.

EYE

Eye examinations included determination of visual acuity, intraocular pressure and extraocular muscle function as well as external and ophthalmoscopic examination. Myopic refractive errors of more than 1.00 diopter were considered departures in the direction of the syndrome. The number of heterozygous carriers and homozygous normal individuals who were found to be myopic, hyperopic, and with miscellaneous insignificant ocular findings is given in table 1.

TABLE 1.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND EYE DEPARTURES IN THE DIRECTION OF THE SYNDROME

Numbers in column under "Misc." represents individuals with miscellaneous insignificant ocular findings. Column under "Ratio" indicates the ratio between the observed number of individuals with eye departures in the direction of the syndrome and the number expected in a random population. *Carrier* refers to heterozygotes who have one normal gene and one gene for spherophakia-brachymorphia. *Normal* represents normal homozygotes who are not known to carry any genes for the syndrome.

Group	Sex	Myopia	Hyperopia	Misc.	Total	Ratio
Carrier	♂	5	1	10	16	2.8
Carrier	♀	7	1	6	14	4.5
Normal	♂	1	2	13	16	.6
Normal	♀	2	1	10	13	1.4

Among 16 heterozygous males, 5 had eye departures in the direction of the syndrome (1-79, 1-124, 1-154, 1-165b, and 1-188), 1 had hyperopia (1-58), and 10 had miscellaneous ocular findings (1-26, 1-54, 1-59, 1-153, 1-158, 1-159, 1-165d, 1-185, 1-192, and 2-27). (Note: Reference numbers to individuals correspond to those used in all figures and tables. The first digit of a reference number, set off by a hyphen, refers to pedigree 1 or 2.) Among 14 heterozygous females, 7 had eye departures in the direction of the syndrome (1-83, 1-100, 1-151, 1-152, 1-157, 1-161, and 2-23), 1 had hyperopia (1-191), and 6 had miscellaneous ocular findings (1-66, 1-165a, 1-165c, 1-168, 2-15, and 2-18). Eye departures in the direction of the syndrome occurred 3.6× the frequency expected in the general population (12 ÷ $^{3}\%_{9}$) when the two sexes were combined.

Among 16 homozygous normal males, 1 (1-99) had eye departures in the direction of the syndrome, 2 had hyperopia (1-82 and 1-84), and 13 had miscellaneous ocular findings (1-29, 1-86, 1-114b, 1-114c, 1-114d, 1-131a, 1-131b, 1-137, 1-138, 1-144, 2-9, 2-12, and 2-17). Among 13 homozygous normal females, 2 had eye departures in the direction of the syndrome (1-69, and 1-136), 1 had hyperopia (1-81), and 10 had miscellaneous ocular findings (1-71, 1-77, 1-85, 1-114a, 1-119, 1-160a, 1-169, 1-193, 2-16, and 2-20). Spherophakia was probably present in (1-136). Eye departures in the direction of the syndrome occurred in almost exactly the same proportion as expected in the general population (3 ÷ $^{29}\%_{9}$ = .9) when the two sexes were combined.

The probability of finding as many as 12 individuals out of a sample of 30 with eye departures in the direction of the syndrome would be expected less than once in 17,000 in a randomly selected population. Consequently, an eye departure in the direction of the syndrome is believed to be one of the stigmata of heterozygous carriers.

STATURE

According to Watson and Lowrey (1951) 17-year-old American males have a mean stature of 176.6 ± 5.8 cm. and 17-year-old females have a mean stature of 165.5 ± 5.1 cm. Using these figures as norms a *short* adult is defined in this study as having a stature between one and two standard deviations below the mean which for males is 165.1 to 170.8 cm. and for females is 155.4 to 160.4 cm. A very short adult has a stature of two or more standard deviations below the mean which for males is 165.0 cm. and for females is ≤155.3 cm. Means and standard deviations for lower age levels may be used to classify individuals under 17 into groups of short, very short and average stature. In a random population of Americans one would expect approximately $\frac{1}{7}$ to be short and $\frac{1}{44}$ to be very short. The range, mean and standard deviation of stature values for the various groups are given in table 2.

The statures of the 3 cases of spherophakia-brachymorphia reported in this study and the statures of 5 previously reported adult males ranged from 145 to 163 cm. with a mean and standard deviation of 153.5 ± 5.5 cm. The stature of 9 fully affected adult females, based on 2 cases reported in this study and 7 previously reported, ranged from 138 to 161 cm. with a mean of 145.6 ± 9.2. Thus all cases with the full syndrome were very short with the exception of 2 females who were one standard

TABLE 2.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND STATURE

Syndrome refers to affected homozygotes who have two genes for the syndrome. *Carrier* refers to heterozygotes who have one normal gene and one gene for spherophakia-brachymorphia. *Normal* represents normal homozygotes who are not known to carry any genes for the syndrome. Values for the "control" group were obtained from Watson and Lowrey (1951).

Group	New Cases	Previously Reported	Total	Sex	Range (cm)	Mean and Standard Deviation
Syndrome	3	5	8	♂	145–163	153.5 ± 5.5
Syndrome	2	7	9	♀	138–161	145.6 ± 9.2
Carrier	7	5	12	♂	153–170	162.6 ± 4.8
Carrier	10	6	16	♀	133–162	151.8 ± 7.1
Normal	8		8	♂	159–176	169.2 ± 6.2
Normal	7		7	♀	157–166	159.4 ± 4.4
Control			100	♂		176.6 ± 5.8
Control			100	♀		165.5 ± 5.1

deviation below the mean, instead of two or more. People with very short stature occurred 38.8 × the frequency expected in the general population (15 ÷ $^{17}/_{44}$).

The statures of 7 heterozygous adult males (1-44, 1-104, and with age adjustments 1-153, 1-154, 1-163, 1-165b, and 1-192) plus the statures of 5 previously reported fathers of fully affected offspring, ranged from 153 to 170 cm. (4 short, 8 very short) with a mean of 162.6 ± 4.8. The statures of 10 heterozygous adult females (1-80, 1-100, 1-151, 1-152, 1-161, 1-168, 2-15, 2-18, 2-23, and with age adjustment 1-191) plus statures of 6 previously reported mothers of fully affected offspring, ranged from 133 to 162 (4 short, 11 very short, 1 average) with a mean of 151.8 ± 7.1. Very short stature occurred 29.9 × the frequency expected by chance (19 ÷ $^{28}/_{44}$).

The statures of 8 normal homozygous adult males (1-99, 1-114b, 1-114c, 1-114d, 1-164b, 2-9, 2-12 and 2-17) ranged from 159 to 176.0 (2 short, 2 very short, 4 average) with a mean of 169.2 ± 6.2. The statures of 7 normal homozygous adult females (1-71, 1-114a, 1-164a, 1-169, 2-16, 2-20, and with age adjustment 164c) ranged from 157 to 166 (3 short, 1 very short, 3 average) with a mean of 159.4 ± 4.4.

The means and variances of various groups were compared with one another to determine whether differences between them were statistically significant (table 3).

With the exception of comparison 1, the stature of males was significantly higher than that of females in all comparisons and the size of the standard deviations in the sexes was similar (comparisons 1, 4, 7 and 12). It would seem that the sexes should be considered separately in all comparisons. The presence of 2 genes for spherophakia-brachymorphia in contrast to one gene would appear to shorten stature in males but not in females (comparisons 2 and 3). A single gene seemed to lower the stature of both males and females (comparisons 5, 6, 8 and 9). The stature of normal males and females was lower than the stature of the control groups (comparisons 10 and 11). The standard deviation of carrier females was larger than the standard deviation of control females, possibly because several individuals were so very short.

The fact the normal homozygotes in these families were shorter than the controls could be due to: (1) bias of investigators in selection of members for measurements, (2) other genes or environmental factors causing an undue amount of shortness in

TABLE 3.—VALUES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES IN STATURE AND SIZE OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS AS DESCRIBED IN TABLE 2

Number	Groups Compared	Degrees Freedom ($n_1 + n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀♀	15	2.0	2.8
2	Syndrome ♂♂ and carrier ♂♂	18	3.7**	1.4
3	Syndrome ♀♀ and carrier ♀♀	23	1.8	1.8
4	Carrier ♂♂ and carrier ♀♀	26	4.4**	2.1
5	Carrier ♂♂ and normal ♂♂	18	2.5*	1.7
6	Carrier ♀♀ and normal ♀♀	21	2.5*	2.4
7	Normal ♂♂ and normal ♀♀	13	3.2**	1.9
8	Carrier ♂♂ and control ♂♂	110	8.0**	1.4
9	Carrier ♀♀ and control ♀♀	114	9.3**	2.0*
10	Normal ♂♂ and control ♂♂	106	3.4**	1.3
11	Normal ♀♀ and control ♀♀	105	3.1**	1.2
12	Control ♂♂ and control ♀♀	198	14.3**	1.3

* .05 level of significance.
** .01 level of significance.

these families, (3) failure to detect carriers who were falsely classified in the normal group, or (4) use of a control group which was not adequate. In World War I men from the part of the United States in which these kindreds live had a stature of 172.6 ± 6.8 according to Davenport and Love (1921).

FINGER-PALM INDEX

The average finger length of a person was determined by measuring the length of each finger on each hand from outline drawings and dividing by 10. See figure 3 for an illustration of distal and proximal points on the fingers for determining finger length. Proximal limits for fingers I, II and V were determined by the intersection of perpendicular lines drawn from most proximal interdigital boundaries and lines extended from most distal finger tips through axes of fingers. Proximal limits for fingers III and IV were determined by intersection of lines connecting most proximal interdigital boundaries and lines extended from most distal finger tips through axes of fingers.

The finger-palm index was obtained by dividing the average finger length of both hands by the average palm width of both hands and multiplying by 100. Palm width was also measured from the hand outlines (see line m–n in figure 3). The range, mean and standard deviation of finger-palm indexes obtained in this study are given in table 4. The means and variances of various groups were compared with one another to determine whether differences between them were statistically significant. See table 5 for the results of these comparisons.

The mean finger-palm index for 55 males and females (31 normal homozygotes and 24 unrelated controls) was 77.8 ± 4.8. Using these figures as norms short fingers are defined as a finger-palm index value between one and two standard deviations

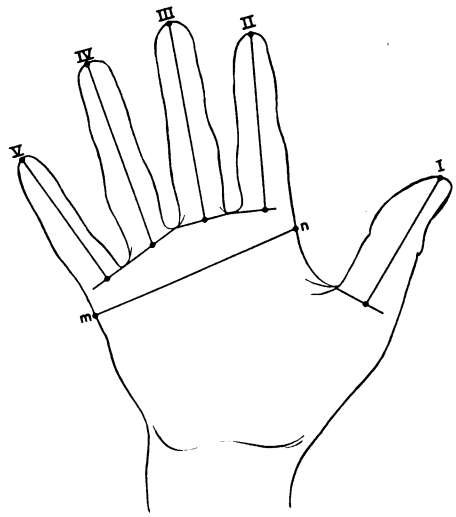

FIG. 3. Outline of hand to illustrate measurements of finger length and palm width. Proximal limits for fingers were determined by the indicated lines, and finger lengths were measured from these lines to ends of the digits. The line m-n shows the level at which palm width was measured.

TABLE 4.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND FINGER-PALM INDEX

Finger-palm index is: (average finger length × 100) ÷ average hand width. Except for three individuals the control group was selected from a population in which one or more relatives carried a gene for sickle-cell anemia.

Group	Number	Sex	Range	Mean and Standard Deviation
Syndrome	3	♂	57–69	63.5 ± 5.0
Syndrome	2	♀	55–58	56.5 ± 1.9
Syndrome	5	♂ and ♀	55–69	60.7 ± 5.3
Carrier	14	♂	62–81	71.1 ± 4.3
Carrier	15	♀	68–80	74.9 ± 3.8
Carrier	29	♂ and ♀	62–81	73.1 ± 4.5
Normal	15	♂	70–86	75.6 ± 3.9
Normal	16	♀	72–86	78.0 ± 3.6
Normal	31	♂ and ♀	70–86	76.8 ± 3.9
Control	12	♂	68–94	78.2 ± 6.4
Control	12	♀	74–85	80.3 ± 4.0
Control	24	♂ and ♀	68–94	79.2 ± 5.5

below the mean, which is 68.27 to 73.05 in this study. Very short fingers are two or more standard deviations below the mean, which is ≤ 68.26.

The finger-palm indexes of the 5 cases of spherophakia-brachymorphia syndrome reported in this study ranged from 55 to 69 with a mean of 60.7 ± 5.3.

Among 14 heterozygous males, 4 had very short fingers 1-154, 1-165b, 1-165d, and 1-192; 8 had short fingers (1-44, 1-58, 1-124, 1-153, 1-158, 1-159, 1-163, and 1-185); 2 had average length fingers (1-79, and 1-104). Finger-palm index values ranged from 62 to 81 with a mean of 71.1 ± 4.3. Among 15 heterozygous females, 1 had very

TABLE 5.—VALVES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES IN FINGER-PALM INDEXES AND SIZE OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS

Number	Groups Compared	Degrees Freedom ($n_1 - n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀ ♀	3	1.5	5.4
2	Syndrome ♂♂ and carrier ♂♂	15	2.5*	1.9
3	Syndrome ♀ ♀ and carrier ♀ ♀	15	6.4**	2.2
4	All syndromes and all carriers	32	5.4**	1.7
5	Carrier ♂♂ and carrier ♀ ♀	27	2.5*	1.3
6	Carrier ♂♂ and normal ♂♂	27	2.9**	1.2
7	Carrier ♀ ♀ and normal ♀ ♀	29	2.3*	1.1
8	All carriers and all normals	58	3.4**	1.3
9	Normal ♂♂ and normal ♀ ♀	29	1.7	1.2
10	Carrier ♂♂ and control ♂♂	24	3.2**	2.3
11	Carrier ♀ ♀ and control ♀ ♀	25	3.4**	1.2
12	All carriers and all controls	51	5.1**	1.5
13	Normal ♂♂ and control ♂♂	25	1.3	2.8*
14	Normal ♀ ♀ and control ♀ ♀	26	1.5	1.3
15	All normals and all controls	53	1.9	1.9
16	Control ♂♂ and control ♀ ♀	22	.9	2.5

* .05 level of significance.
** .01 level of significance.

short fingers (1-168); 6 had short fingers (1-40, 1-66, 1-109, 1-152, 1-191, and 2-15); 8 had average or long fingers (1-80, 1-83, 1-100, 1-151, 1-157, 1-161, 2-18, and 2-23). Finger-palm index values ranged from 60 to 80 with a mean of 74.9 ± 3.8.

Among 15 homozygous normal males, 3 had short fingers (1-84, 1-86, and 1-114b); 12 had average or long fingers (1-82, 1-99, 1-114c, 1-114d, 1-131a, 1-131b, 1-137, 1-164b, 1-186a, 2-9, 2-12 and 2-17). Finger-palm index values ranged from 70 to 86 with a mean of 75.6 ± 3.9. Among 16 homozygous normal females, 1 had short fingers (1-193); 15 had average or long fingers (1-34, 1-45, 1-69, 1-71, 1-77, 1-81, 1-85, 1-93, 1-114a, 1-136, 1-160a, 1-164a, 1-164c, 1-169, and 2-16). Finger-palm index values ranged from 72 to 86 with a mean of 78.0 ± 3.6.

Although the finger-palm index values for males and females in comparison 1 did not differ significantly, the number of individuals in these groups was inadequate. Likewise, when these two groups were used for comparisons 2, 3 and 4 they were too small to assure valid results, but if similar values were to be obtained with larger numbers one might conclude that the presence of two genes in contrast to one gene shortened the fingers in both males and females. In like manner a single gene seems to shorten the fingers in both sexes in contrast to no gene for the syndrome (comparisons 6, 7, 8, 10, 11, and 12). When spherophakia-brachymorphia genes were absent non-significant t and F values were obtained in the sexual comparisons (9 and 16), but when a single gene was present the mean finger-palm index seemed to be lowered more in males than in females (comparison 5). Since the normal are all relatives from two families possibly they are more homogeneous than the controls taken from many families and this difference is reflected in the high F-value obtained in comparisons 13.

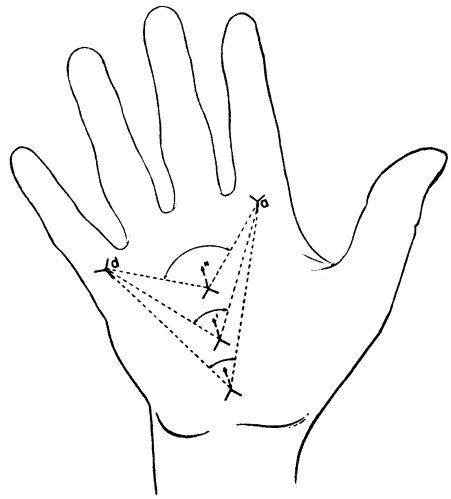

FIG. 4. The *atd* angle is described by the intersection of dotted lines extended from the a and d digital triradii to the highest axial triradius on the palm which may be located in the t, t′, or t″ position. A triradius is formed by epidermal ridges running in three directions past a common point.

atd ANGLE AND POSITION OF AXIAL TRIRADIUS

Epidermal ridges running in 3 directions past a common point form a triradius which when located at or very near the proximal margin of the palm is in the t position (figure 4). Axial triradii located near the transverse flexion crease in the middle of the palm are in the t″ position, the most distal or highest position in which axial triradii are located. Axial triradii located in the intermediate area between t″ and t are called t′. The symbol 0 signifies absence of any axial triradius.

In none of the 10 hands of the 5 fully affected cases (table 6) was the highest axial triradius as low as the most common t position. In one person the highest position on each hand was t′ and in each of the remaining 8 hands the highest position was t″ which was 10 × the number expected according to the frequency distribution of 1,281 German males reported by Cummins and Midlo (1943). In their study the position of the most distal axial triradius appeared in the t, t′, or t″ position with a

TABLE 6.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND POSITION OF HIGHEST AXIAL TRIRADIUS

See figure 4 for illustration of position of axial triradius. Control values are from a study of 1281 German males reported by Cummins and Midlo (1943).

Highest Axial Triradius	Control	Syndrome		Carrier		Normal	
		Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
t″	8.3	8	.8	13	5.2	3	6.0
t′	28.0	2	2.8	21	17.3	12	20.1
t	62.9	0	6.3	26	39.0	57	43.3
0	.8	0	.1	2	.5	0	.6
Total	100.0	10	10.0	62	62.0	72	72.0

frequency of 62.9, 28.0 and 8.3 percent, respectively, and there was no triradius (0) in only 0.8 percent of the hands.

In 13 of the 62 hands of heterozygotes the highest triradial position was in the t″ position which is approximately 2.5 × the number expected. Three of the 72 hands of normal homozygous individuals had a triradius in the t″ position which is half the expected number and is not significant.

Cummins (1939) first noted the occurrence of t″ in the palms of mongoloids to be 8 times the frequency found in any known racial group and suggested that the position of the axial triradius might be a useful sign in the diagnosis of mongolism. We are indebted to this same author for first calling to our attention the high frequency of t″ in the palms of individuals possessing genes for the spherophakia-brachymorphia syndrome.

Penrose (1954) demonstrated the value of using the *atd* angle (fig. 4) in the study of mongolism. In a control population of 510 adult males and 507 adult females he reported the mean and standard deviation of the *atd* angles (based on the sum of the largest *atd* angle in the right and left hands): 85.04 ± 15.27° in males and 85.93 ± 15.70° in females. Corresponding values for lower age groups were found to be for 28 males 0–4 years of age 92.54 ± 14.15°, for 483 males 5–14 years of age 88.14 ± 15.86°, for 32 females 0–4 years of age 97.67 ± 19.64°, and 486 females 5–14 years of age 89.81 ± 17.27°, respectively.

As in stature large and very large *atd* angles may be defined to be from one to two, and two or more standard deviations above the mean, respectively. Large and very large *atd* angles would be expected to occur in approximately 1/7 and 1/44 individuals, respectively, selected at random from a normal population. In terms of the values found by Penrose a large *atd* angle would range in males from 100.32 to 115.57° and for females from 101.63 to 117.32°. Very large *atd* angles for males would be ≥115.58 and for females ≥117.33. The range, mean and standard deviation for size of *atd* angles in the various groups are given in table 7.

TABLE 7.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND SIZE OF *atd* ANGLE

The size of the *atd* angle used is the sum of the largest *atd* angle (figure 4) on the right and left palms. Control values are from Penrose (1954).

Group	Number	Sex	Range (degrees)	Mean and Standard Deviation
Syndrome	3	♂	119.0–128.5	124.8 ± 4.2
Syndrome	2	♀	145.5–158.5	152.0 ± 6.5
Syndrome	5	♂ and ♀	119.0–158.5	135.7 ± 14.3
Carrier	16	♂	77.0–147.9	103.5 ± 20.1
Carrier	12	♀	82.0–136.6	102.2 ± 20.5
Carrier	28	♂ and ♀	77.0–147.9	102.9 ± 20.3
Normal	14	♂	75.0– 89.0	80.5 ± 4.3
Normal	17	♀	76.5–118.0	90.8 ± 10.9
Normal	31	♂ and ♀	75.0–118.0	86.2 ± 10.0
Control	510	♂	55.0–160.0	85.0 ± 15.3
Control	507	♀	55.0–150.0	85.9 ± 15.7
Control	1017	♂ and ♀	55.0–160.0	85.5 ± 15.5

The *atd* angles of 3 adult males with spherophakia-brachymorphia ranged from 119 to 128.5° with a mean and standard deviation of 124.8 ± 4.2°. The corresponding values for two fully affected females ranged from 145.5 to 158.5° with a mean and standard deviation of 152.0 ± 6.5°. In every case the *atd* angle was very large with an occurrence 44 times the frequency expected in the general population (5 ÷ 5/44).

The *atd* angles of 16 adult carrier males ranged from 77° to 147.9° with a mean and standard deviation of 103.5 ± 20.1. Among these 16 carrier males, 5 had very large *atd* angles (1-79, 1-154, and with age adjustments, 1-124, 1-165b, 2-27); with age adjustments 3 had large *atd* angles (1-159, 1-165d, and 1-188); 8 had average size *atd* angles (1-44, 1-58, 1-104, 1-153, 1-163, and with age adjustments 1-158, 1-185, 1-192). The values for 12 females ranged from 82 to 136.6° with a mean and standard deviation of 102.2 ± 20.5. Among these 12 carrier females, 2 had very large *atd* angles (1-100, and with age adjustment 1-157); 3 had large *atd* angles (1-83, 1-151, and 2-18); 7 had average size *atd* angles (1-66, 1-152, 1-161, 1-168, 2-15, 2-23, and with age adjustment 1-191). Very large *atd* angles occurred 11.0 × the frequency expected in the general population (7 ÷ 28/44) and large or very large *atd* angles occurred 3.3 × the frequency expected in the general population (13 ÷ 28/7).

The *atd* angles of 14 normal homozygous adult males ranged from 75 to 89° with a mean and standard deviation of 80.5 ± 4.3°. (These 14 males included 1-82, 1-84, 1-86, 1-99, 1-114b, 1-114c, 1-114d, 1-131a, 1-164b, 2-9, 2-12, 2-17 and with age adjustments 1-131b, and 1-137.) The values for 17 normal females ranged from 76.5 to 118° with a mean and standard deviation of 90.8 ± 10.9°. (These 17 females included 1-34, 1-69, 1-71, 1-77, 1-81, 1-85, 1-93, 1-114a, 1-119, 1-164a, 1-169, 2-16, 2-20, and with age adjustments 1-136, 1-160a, 1-164c and 1-193.) All 14 normal males had average size *atd* angles. Among the 17 normal females, one had very large (1-114a), two had large (1-85, and 1-119) and 14 had average size *atd* angles. Very large *atd* angles occurred 1.4 times the frequency expected in the general population (1 ÷ 31/44) and large or very large *atd* angles occurred 0.7 times the frequency expected in the general population (3 ÷ 31/7).

The mean and variances of various groups were compared with one another to determine whether or not differences between them were statistically significant. With few exceptions the t and F values summarized in table 8 were found to be similar to those obtained for stature.

The *atd* angles in individuals with the syndrome were larger in females than in males, but the size of these groups was too small for a valid statistical comparison (comparison 1). Likewise, when these two groups were used for comparisons 2, 3 and 4 they were too small to assure valid results, but if similar values were to be obtained with larger numbers one might conclude that the presence of two genes for the syndrome in contrast to one or none increases the size of *atd* angles (comparisons 3 and 4).

The larger *atd* angles observed in normal females than in normal males (comparison 9) were probably fortuitous since such a difference was not found among heterozygotes (comparison 5) or among the controls (comparison 16).

In contrast to the normal and control groups the presence of a single gene for spherophakia-brachymorphia seemed to increase the size of *atd* angles (comparisons 6,

TABLE 8.—VALUES OF t AND F OBTAINED FROM TESTS OF SIGNIFICANCE APPLIED TO DIFFERENCES OF *atd* ANGLES AND OF STANDARD DEVIATIONS AMONG THE VARIOUS GROUPS

Number	Groups Compared	Degrees Freedom ($n_1 + n_2 - 2$)	t-value	F-value
1	Syndrome ♂♂ and syndrome ♀♀	3	4.4*	3.2
2	Syndrome ♂♂ and carrier ♂♂	17	1.7	16.6
3	Syndrome ♀♀ and carrier ♀♀	12	3.2**	5.4
4	All syndromes and all carriers	31	3.4**	1.7
5	Carrier ♂♂ and carrier ♀♀	26	.2	1.1
6	Carrier ♂♂ and normal ♂♂	28	4.1**	21.4**
7	Carrier ♀♀ and normal ♀♀	27	1.9	3.7**
8	All carriers and all normals	57	4.0**	4.2**
9	Normal ♂♂ and normal ♀♀	29	3.2**	6.2**
10	Carrier ♂♂ and control ♂♂	524	4.7**	1.8*
11	Carrier ♀♀ and control ♀♀	517	3.5**	1.9*
12	All carriers and all controls	1043	5.8**	1.8**
13	Normal ♂♂ and control ♂♂	522	1.1	11.6**
14	Normal ♀♀ and control ♀♀	522	1.3	2.0*
15	All normals and all controls	1046	.1	2.3**
16	Control ♂♂ and control ♀♀	1015	.9	1.1

* .05 level of significance.
** .01 level of significance.

8, 10, 11, 12). The value obtained in comparison number 7 between heterozygous females and normal females was not statistically significant due possibly to (1) other genes or environmental factors causing large *atd* angles in these females, or (2) failure to detect heterozygotes who were falsely classified in the normal group.

The variance in *atd* angles as indicated by significant and highly significant F-values was larger in heterozygotes (males and females) than in the normal or control groups (comparisons 6, 7, 8, 10, 11, 12). The variance in normal males was less than that of control males (comparisons 13, 14, 15). This may be because males belonging to two kindreds were more homogeneous for genes not associated with the syndrome than individuals selected at random. The smaller variance in normal males than in normal females (comparison 9) must be fortuitous.

SPAN INDEX

Span index was obtained by dividing span by height and multiplying by 100. The range, mean, and standard deviation for the span index values in the various groups are listed in table 9, but the numbers of individuals in most of the groups are too small for statistical comparisons. The values for all individuals believed to carry one or two genes were reduced and this is in the direction expected if "shortened extremities" are also a stigma of the syndrome.

There was one statistically significant difference among the various groups. The mean and standard deviation for the span of all 5 affected individuals was 93.4 ± 3.1 and the corresponding values for all 15 carriers was 98.8 ± 3.2. The t-value for the difference in these two groups was 3.0 which with 18 degrees of freedom would be

TABLE 9.—SPHEROPHAKIA-BRACHYMORPHIA GENE AND SPAN INDEX

Span index = (span × 100) ÷ stature.

Group	Number	Sex	Range	Mean and Standard Deviation
Syndrome	3	♂	89.0– 97.7	94.3 ± 3.8
Syndrome	2	♀	91.7– 92.4	92.0 ± .3
Syndrome	5	♂ and ♀	89.0– 97.7	93.4 ± 3.1
Carrier	8	♂	91.9–106.9	99.9 ± 4.0
Carrier	7	♀	94.1–100.8	98.8 ± 2.4
Carrier	15	♂ and ♀	91.9–106.9	98.8 ± 3.2
Normal	8	♂	98.0–106.7	101.6 ± 2.5
Normal	6	♀	95.0–104.0	99.0 ± 2.9
Normal	14	♂ and ♀	95.0–106.7	100.4 ± 3.0

expected less than once in 100 if the homozygous state of spherophakia-brachymorphia gene has no effect upon span index.

The importance to be attached to low span index for affected individuals is questionable since the value calculated from the data reported by Diethelm (1947) for an affected female was 100.3 and the value calculated from data reported by Stadlin and Klein (1948) for an affected female was 100.0. No control span index values were available to determine how much the values obtained deviate from the mean.

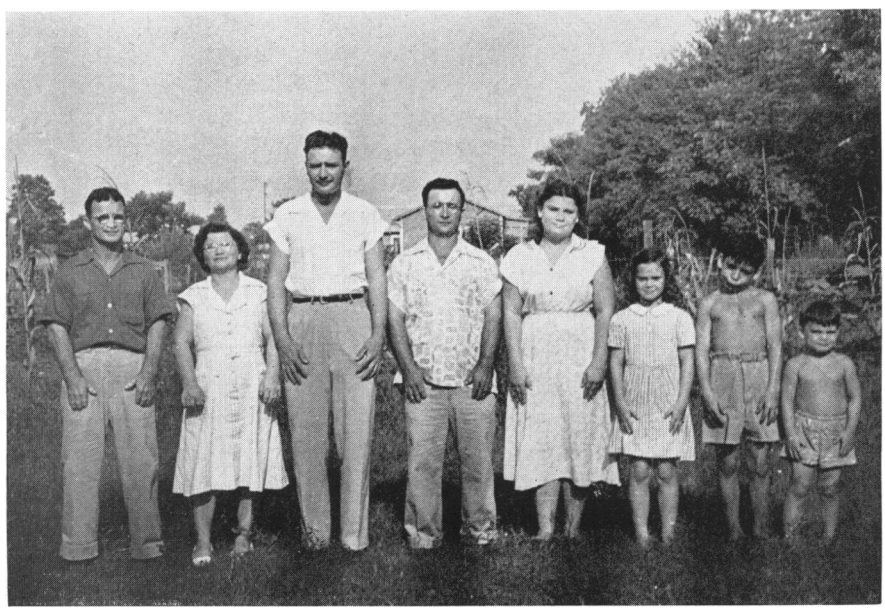

FIG. 5. Individuals in Kindred 1, from left to right are: 1-96, propositus who has recessive type of spherophakia-brachymorphia syndrome; 1-102, homozygous affected sister; 1-99, homozygous normal brother (5′8″ tall); 1-105, homozygous affected brother, 1-105w, homozygous normal wife of 1-105; 1-165c, 1-165b and 1-165d, heterozygous carrier children of 1-105 and 1-105w.

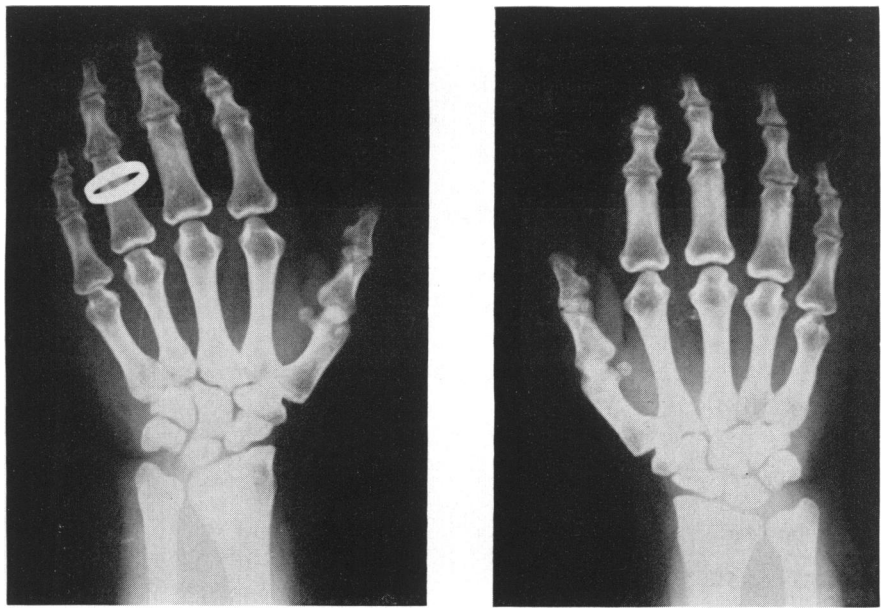

FIG. 6. Brachydactyly in an individual (pedigree number 1-94) who has recessive type of spherophakia-brachymorphia syndrome.

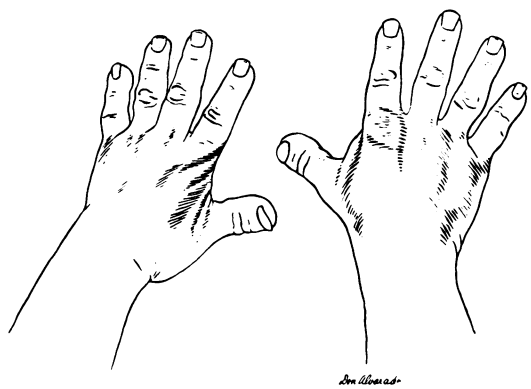

FIG. 7. Brachydactyly in an individual (pedigree number 2-19) who has recessive type of spherophakia-brachymorphia syndrome.

DISCUSSION

In the absence of specific anthropometric data, subjective ratings do not communicate the same impression to all readers. No one previously has attempted to indicate precisely the demarcation between "short" and "average." Deviations from a mean encountered in one out of 7 or one out of 44 from a random population are not particularly obvious. See figures 5–7 for photographs of fully affected individuals. The need of objective measurements is apparent if anthropometric data for various studies are to be combined.

The selection of deviations from the mean in the direction of the syndrome as small or smaller than one would expect to find in 1/9 (eye), 1/20 (stature), 1/7 (finger length) and 1/9 (*atd* angle) of a random population appears to be rather arbitrary but these stigmata do seem to separate 74 relatives of the 5 fully affected homozygotes into one group of 38 heterozygotes and another group of 36 normal homozygotes.

The values reported by Watson and Lowrey (1951) for stature were used as controls because they cover the lower age levels in both sexes. With the use of a control population more appropriate for American families of French descent in this region values deviating as much or more than those occurring in about one in 7 of the population would be equivalent to the one in 20 obtained when tables for stature based on the Iowa study were used. The mean stature of adult males from the areas in which our kindreds live, as reported by Davenport and Love (1921) for World War I enlistees, was 4.0 cm. shorter than the value given by Watson and Lowrey (1951); the Newman (1951) figure for World War II service men at discharge was 2.8 cm. shorter; and the Randall (1949) figure for similarly selected adult females was 3.2 cm. shorter.

The observed association between wide *atd* angle and the gene for spherophakia-brachymorphia might be explained in one of three ways: (1) A wide *atd* angle is one of the stigmata of the syndrome occurring more frequently in both homozygous affected and heterozygotes than in normal homozygotes. (2) A gene contributing to wide *atd* angle might exist and be located on the same pair of chromosomes as the gene for the syndrome. If these two genes were on the same chromosome in a large family in which most of the observations were made, both might tend to be present in the same individuals and to be absent in others. If this explanation be true one would not expect this association to occur in more than half of the families segregating for both the spherophakia-brachymorphia syndrome and wide *atd* angle depending upon the repulsion or coupling phase of the genes. (3) A third explanation is that the relationship between the syndrome and wide *atd* angle is fortuitous. The genetics of variation in the *atd* angle is unknown. We consider the first explanation the most plausible and thus have treated wide *atd* angle as a stigma of the syndrome.

The omission of wide *atd* angle as a stigma would have caused only four individuals (1-79, 1-83, 2-18, and 2-27) to have been left out of the group of 38 heterozygotes listed in tables 10 and 11. In like manner the omission of stigmata for stature, finger-palm index or eye departures in the direction of the syndrome would have caused 16, 12 or 2 respectively, to have been left out of the heterozygous group.

Among 74 observed relatives of the 5 fully affected individuals, 38 were heterozygous and 36 (used in calculations) were homozygous normal according to the criteria described previously for selection of heterozygotes. With one exception (1-80 who was 133.4 cm. tall, a height this short or shorter to be expected once in a million) the criteria were adhered to strictly in spite of the fact that specific information about one or more stigmata was lacking in many cases. In addition, 17 relatives were observed but precise measurements were not made. It is our opinion that among these 17 observed relatives, 3 were heterozygous (1-54, 1-165e, and 1-165f), 1 was homozygous normal (1-16), and 13 could not be classified (1-160b, 1-186e,

TABLE 10.—STIGMATA FOUND IN HETEROZYGOUS MALES

Stigma present, ×; stigma absent, 0; information about stigma missing, ? Column A represents assumed heterozygotes because they were (1) offspring or parents of fully affected homozygotes or (2) the parents of a heterozygous child and related to propositus. Column B represents heterozygotes who possessed two or more stigmata of the syndrome. Column C represents individuals who would have been placed in homozygous normal group had the particular stigma above the column not been observed. Final column gives approximated probability of encountering an individual in a random population with stigmata deviating as much or more in the direction of the syndrome if stigmata are uncorrelated within individuals.

Pedigree Number	Eye			Short Stature			Short Fingers			Wide *atd* Angle			Probability
	A	B	C	A	B	C	A	B	C	A	B	C	
1-26	0			×			×			?			7.1×10^{-3}
1-44		?			×	×		×	×		0		1.5×10^{-3}
1-58		0			×	×		×	×		0		4.2×10^{-3}
1-59		0			×			×			×		1.4×10^{-4}
1-64		?			×	×		×	×		0		5.5×10^{-4}
1-79		×	×		0			0			×	×	7.8×10^{-4}
1-104	?			×		×	0			0			2.0×10^{-3}
1-124		×			×			×			×		2.1×10^{-6}
1-140		?			×	×		×	×		?		5.5×10^{-4}
1-148	?			×		×	?			?			5.0×10^{-2}
1-153	0			×			×			0			4.0×10^{-4}
1-154	×			×			×			×			5.8×10^{-10}
1-158		0			×	×		×	×		0		8.6×10^{-4}
1-159		0			×			×			×		4.8×10^{-4}
1-163		?			×	×		×	×		0		1.3×10^{-3}
1-165b	×			×			×			×			1.0×10^{-9}
1-165d	0			×			×			×			4.2×10^{-7}
1-185		0			×	×		×	×		0		1.3×10^{-3}
1-188		×			×			?			×		9.9×10^{-5}
1-192		0			×	×		×	×		0		6.5×10^{-4}
2-27		0			×	×		?			×	×	1.1×10^{-3}
Total	2	3	1	7	13	11	5	11	8	3	6	2	
Percent	40.0	30.0	4.8	100.0	92.9	52.4	83.3	91.7	38.1	60.0	46.2	9.5	

1-186f, 1-186g, 1-189, and 1-190 who were 3 months to 3 years old; 1-48, 1-90, 1-108a, 1-108b, 1-186b, 1-186c, 1-186d who were over 3 years old).

Among 39 individuals who were not observed, 1-97 would have become fully affected according to relatives, 25 were probably heterozygous (1-1, 1-8, 1-10, 1-11, 1-12, 1-14, 1-17, 1-20, 1-23, 1-25, 1-28, 1-35, 1-37, 1-39, 1-41, 1-42, 1-47, 1-65a, 1-65b, 1-87, 1-91, 150a, 150b, 2-7, 2-8), and 13 were most likely homozygous normal (1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-15, 1-19, 1-36, 1-38, 1-51, 1-53, and 2-24) according to pedigree relationships and reported information. An additional 738 relatives were not observed or classified.

The authors are well aware that an association between two traits in an individual is no proof that the two traits are causally related to one another or to a third cause

TABLE 11.—STIGMATA FOUND IN HETEROZYGOUS FEMALES

Sitgma present, ×; stigma absent, 0; information about stigma missing, ? Column A represents assumed heterozygotes because they were (1) offspring or parents of fully affected homozygotes or (2) the parents of a heterozygous child and related to the propositus. Column B represents heterozygotes who possessed two or more stigmata of the syndrome. Column C represents individuals who would have been placed in homozygous normal group had the stigma above the column not been observed. Final Column gives approximated probability of encountering an individual in a random population with stigmata deviating as much or more in the direction of the syndrome if the stigmata are uncorrelated within individuals.

Pedigree Number	Eye			Short Stature			Short Fingers			Wide *atd* Angle			Probability
	A	B	C	A	B	C	A	B	C	A	B	C	
1-40		?			×	×		×	×		?		1.0×10^{-3}
1-66	0			×			×			0			1.9×10^{-6}
1-80		?			×	×		0			?		1.0×10^{-7}
1-83		×	×		?			0			×	×	9.0×10^{-4}
1-100	×			×			0			×			5.0×10^{-8}
1-109		?			×	×		×	×		?		2.3×10^{-6}
1-151	×			×			0			×			1.1×10^{-5}
1-152	×			×			×			0			2.3×10^{-4}
1-157		×			×			0			×		1.0×10^{-7}
1-161	×			×			0			0			7.4×10^{-4}
1-165a	0			×			×			?			7.1×10^{-3}
1-165c	0			×			×			?			7.1×10^{-3}
1-168	0			0			×		×	0			1.5×10^{-3}
1-191		0			×	×		×	×		0		1.4×10^{-3}
2-15	0			×			×			0			1.3×10^{-8}
2-18		0			×	×		0			×	×	3.3×10^{-3}
2-23	×			×			0			0			7.4×10^{-4}
Total	5	2	1	9	6	5	6	3	4	2	3	2	
Percent	50.1	50.0	5.9	90.0	100	29.4	60.0	42.9	23.5	25.0	75.0	11.8	

(gene). Yet, when short stature and short fingers have been observed to be associated with the eye condition described in the spherophakia-brachymorphia syndrome on so many different occasions the most plausible explanation is that some common gene is causing both traits even though genes at various loci are believed to contribute normally to these variations. One would expect the effects of the gene in spherophakia-brachymorphia to vary according to the presence of genes normally contributing to variation in these traits. This same generalization might be made for the values obtained for the other stigmata. However, unless associations between these stigmata occur in the general population (no significant correlation was found between finger-palm index and stature), one would not expect to find so many constellations of these stigmata in so many individuals chosen from a random population.

Tables 10, 11, and 12 give the frequencies of stigmata in heterozygous males and females and of the particular combinations observed in the various individuals. Had data been complete in every case for all 4 stigmata, many of the probabilities of

TABLE 12.—FREQUENCY* OF STIGMATA IN HETEROZYGOTES

The stigmata represented in the first column are eye departures in the direction of the spherophakia-brachymorphia syndrome, short stature, short fingers and wide *atd* angle.

Stigma	Males			Females			Males and Females		
	Number	Number with stigma	Percent with stigma	Number	Number with stigma	Percent with stigma	Number	Number with stigma	Percent with stigma
Eye	16	5	31.3	14	7	50.0	30	12	40.0
Stature	26	24	92.3	22	20	90.9	48	44	91.7
Fingers	18	16	88.9	17	9	52.9	35	25	71.4
atd angle	19	9	47.4	12	5	41.7	31	14	45.2

* Exclusive of duplications the individuals used in the preparation of this table include those used in the derivation of statistical values and those listed in tables 10 and 11.

encountering at random such a group of stigmata in the direction of the syndrome would undoubtedly be higher, and perhaps some classed as normal in Tables 13–14 would need to be transferred to the heterozygous group. So many high values for these probabilities even when adjustments are made for a more adequate control population suggest that something other than chance must have caused the stigmata to be present in these particular relatives. Had time permitted examination of relatives in other branches of the kindreds, many more heterozygous carriers would undoubtedly have been found. In most cases the selection of particular branches for study was dependent upon proximity of individuals to the examiners. Since most cases thought by relatives to be deviating to an extreme degree in the direction of the syndrome were checked, other cases of the full syndrome are not considered to occur in these two kindreds, although there is good reason to believe from reports by relatives that had 1-97 lived, he too would have had the full syndrome for he had brachydactyly as extreme as any of his fully affected siblings.

Short stature, short fingers, wide *atd* angle, and eye abnormalities in the direction of the syndrome were present in all 5 fully affected individuals and they occurred in 91.7, 71.4, 45.2 and 40.0 percent of the heterozygotes, respectively (table 12). These values are also estimates of penetrance for the spherophakia-brachymorphia gene.

The possibility of error in classification of a heterozygote is believed to be about 10%. It should be emphasized that it may not be correct statistically to include individuals in the calculation of penetrance values who were placed in the group because they possessed a particular stigma. When these individuals are omitted (3, 27, 12, and 5 individuals, respectively, for each of the foregoing stigmata), estimates of penetrance become 90.5, 56.5, 38.5, and 37.0 percent. These values do not differ significantly from the preceding estimates.

Since 1 out of 12 assumed heterozygotes (1-168) who were examined for all 4 stigmata possessed only one stigma, it is possible that the standards used for selection of heterozygotes were too severe and some who possess a single stigma and were classed as homozygous normals should be considered heterozygous. The two in the normal group with the lowest probabilities were 2-9 and 2-17. However, it was felt better to err on the conservative side, and except for assumed heterozygotes and 1-80, the presence of two stigmata was considered necessary to identify a heterozygote.

Stigmata were present in the following combinations in the group of 17 assumed heterozygotes listed in tables 10 and 11: 2 had short stature only (information was lacking in one or three stigmata); 6 had short stature and short fingers (3 lacked information in one stigma); 2 had short stature and eye departures, one had eye departures and wide *atd* angle (information lacking in one stigma); 2 had short stature, eye departures, and wide *atd* angle; one had short stature, short fingers and wide *atd* angles; one had short stature, eye departures, and short fingers; and 2 had all 4 stigmata.

In the group of 21 heterozygotes who possessed two or more stigmata the following combinations were present: 11 possessed short stature and short fingers (6 lacked information for one or two stigmata); two possessed eye abnormalities and wide *atd* angles (one lacked information in one stigma); two possessed short stature and wide *atd* angles (1 lacked information in one stigma); two had eye abnormalities, short stature, and wide *atd* angles (1 lacked information about finger-palm index); two had short stature, short fingers and wide *atd* angles; one had all 4 stigmata; and one (information not known in two stigmata) had an extremely short stature only.

Undoubtedly there are many other stigmata associated with this syndrome in addition to the 4 described in this study. Further study should be given to the stiffness of phalangeal joints and the stiffness of lower limb joints which is present in some affected individuals. The stiffness of the lower limb joints may account for the peculiar walk observed in 1-96, reported by relatives in 1-14, 1-41, 1-165f, and also described in a case by Stadlin and Klein (1948).

Anthropometric values in all 5 individuals with the full syndrome and in 20 to 29 individuals who are normal homozygotes or carriers may be combined with additional data and reported later for the following: sitting height, weight, chest circumference, head height, height of trochlear point, height of anterior superior spine, upper arm length, forearm length, hand length, hand width, femur length, tibia length, ear length, ear width, ear lobes, hair color, handedness, presence of midphalangeal hair, ability to curl tongue, ability to taste P.T.C., direction of hair whorl, ABO, MN, and Rh blood types. Also, palm and finger prints were taken on all individuals in which the size of the *atd* angle is reported. The anthropometric values reported by Diethelm (1947) make a fine model to be followed when anthropometric values are to be obtained in a study of spherophakia-brachymorphia.

Notations were made about the presence of three additional rare traits segregating in these two kindreds. A very large thumb was noted bilaterally in 2-9, 2-19 and 2-20, and a tendency to develop gout was present in 2-7, 2-18 and 2-25a. One or two genes for schizophrenia are believed to be present in the following individuals: 1-10, 1-16, 1-21, 1-23, 1-35, 1-39, 1-47, 1-60e, 1-80, 1-90, 1-109 and 1-146a. Had information about schizophrenia been sought, more individuals with one or two genes for schizophrenia undoubtedly would have been found.

SUMMARY

Two large kindreds, one containing 824 individuals of French descent and the other containing 49 individuals of Italian descent, are presented. Direct observations were made in 96 individuals.

Criteria are presented which were found useful to distinguish 38 heterozygous carriers of the spherophakia-brachymorphia gene from 36 homozygous normals and 5 homozygous affected individuals. With the exception of 17 individuals (8 under 3 years old) information was sufficient to classify all persons observed. Four of these 17 could be placed in heterozygous or normal groups from pedigree relationship and subjective impressions.

Anthropometric stigmata which were found most useful to distinguish the various genotypic groups were short stature, short fingers, and wide *atd* angles.

Range, mean and standard deviation are given for each stigma in each genotypic group, and separately for each sex.

Tests of significance are reported which show that the values obtained for the various groups are statistically significant in spite of the small numbers of individuals in some of the groups.

The penetrance of the gene for the spherophakia-brachymorphia syndrome in heterozygous carriers was found to be 91.7, 71.4, 45.2 and 40.0 percent for short stature, short fingers, wide *atd* angle, and ocular departures from normal in the direction of the syndrome, respectively. In homozygous affected individuals penetrance was 100% for each of these four stigmata.

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APPENDIX

TABLE 13.—DATA FOR INDIVIDUALS IN SPHEROPHAKIA-BRACHYMORPHIA KINDREDS REPRESENTED BY PEDIGREES 1 AND 2

In bilateral observations the value for the right eye or hand appears first. In column under "Classification" the first four digits refer respectively to eye, stature, finger-palm index and *atd* angle. In each of these the status of the stigma is identified by numerals as follows: 1, stigma present; 2, stigma absent; 3, undetermined. The fifth digits indicate: 1—heterozygous carrier (partial syndrome), 2—homozygous normal, 3—undetermined, and 4—homozygous affected (full syndrome). For explanation of stigmata see "Criteria used in selection of heterozygotes."

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with c̄)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width, (mm)	t-tri-radius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-34	65	♀					44	76	81	75	56	90	t	43.0	33222
							60	76	79	75	59	87	t	40.5	
1-40	65	♀			153?		54	64	72	67	52	85			31131
							51	64	72	68	52	84			
1-44	55	♂			165.1		57	67	75	72	54	92	t	37.5	31121
							55	67	78	75	56	93	t	38	
1-45	60	♀			av.		51	70	76	71	55	85	t		32232
							51	71	74	72	53	88	t		
1-58	61	♂	20/15c̄	+1	152?		47	63	73	69	55	88	t	40.5	21121
			20/15c̄				48	68	77	71	56	87	t	45.5	
1-66	46	♀	20/40		144?		48	61	68	65	43	82	t	42.5	21121
			20/20				48	63	70	64	45	79	t	45.0	
1-69	26	♀	20/70	−3	av.		53	73	82	72	58	79	t	38.5	12222
			20/50				55	72	81	74	57	79	t′	44.5	
1-71	43	♀	20/40		160.6		59	71	80	73	53	81	t	42.5	22222
			20/40				58	68	80	73	53	79	t	45.0	
1-77	50	♀	20/200				52	70	80	76	60	88	t	43.5	23222
			20/200				52	72	80	75	58	86	t	43.5	
1-79	55	♂	20/200	−1	177.8?		60	91	100	93	69	99	tt″	76.5	12211
			L.P.				63	84	94	92	72	104	t	46.5	
1-80	49	♀			133.4		47	61	72	69	56	79			31231
							46	62	69	69	79				
1-81	51	♀	20/200	+6			53	71	81	79	61	90	t	38.0	23222
			20/200				55	73	81	79	60	89	t	38.5	
1-82	40	♂	20/20c̄	+2			60	75	85	81	65	99	t	40.5	23222
			20/20c̄				57	79	90	83	66	98	t	37.0	
1-83	43	♀	20/30c̄	−2			51	78	87	79	60	89	0		13211
			20/20c̄				57	74	85	78	59	88	t′	53.5	
1-84	38	♂	20/200	+3	av.		57	72	81	78	61	98	t	38.5	22122
			20/200				54	72	80	77	62	100	t	36.5	
1-85	34	♀	20/15	0	av.		55	70	78	74	58	85	t	40.5	22212
			20/15				51	70	77	71	56	83	tt″	71.0	
1-86	56	♂	20/30				51	71	78	78	58	97	t	36.5	23122
			20/30				56	69	77	75	58	96	t′	40.5	
1-93	50	♀					56	74	81	74	55	85	t	46.5	33222
							49	74	81	73	55	88	t	44.5	
1-94	49	♀			140.7	130.0	42	46	55	57	42	80	t″	74.0	11114
							40	42	53	56	40	82	t″	71.5	
1-96	47	♂			151.1	134.5	41	46	53	60	45	87	t″	66.5	11114
							47	48	57	58	43	87	tt″	60.5	

TABLE 13.—*Cont.*

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with ♀)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width (mm)	t-tri-radius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-99	28	♂	20/20	−4	173.5	172.5	58	73	82	76	61	94	t	40.5	12222
			20/20				58	72	82	76	60	92	t	42.0	
1-100	46	♀	20/70	−6	154.4	154.0	55	70	80	78	55	86	tt″	77.5	11211
			20/70				60	68	77	75	57	82	tt″	72.5	
1-102	41	♀			137.4	126.0	45	43	46	48	42	83	t″	80.5	11114
							41	45	50	52	39	82	t″	78.0	
1-104	42	♂			159.9	171.0	58	74	83	76	61	94	t	37.0	31221
							63	76	84	78	61	90	t′	40.0	
1-105	33	♂			153.0	147.0	48	58	67	66	52	96	tt″	68.0	11114
							56	63	69	67	51	91	tt″	60.5	
1-109	26	♀			142?								t		31111
							41	57	67	60	44	75	t″		
1-114a	24	♀	20/25	0	166.4	173.0	61	82	92	87	68	94	tt″	55.5	22212
			20/20				61	84	92	86	67	92	tt″	62.5	
1-114b	22	♂	20/20	0	176.0	172.5	60	76	86	80	62	100	t	40.0	22122
			20/20				60	80	82	70	54	100	t	41.0	
1-114c	18	♂	20/20	0	175.8	178.0	62	87	93	87	70	104	t	42.0	22222
			20/20				59	85	92	87	67	107	t	43.0	
1-114d	17	♂			173.4	177.0	67	80	87	81	61	97	t	40.0	22222
							62	82	88	80	63	97	t	43.5	
1-119	42	♀	20/200	0									t′	54.0	23312
			20/20										t′	51.0	
1-124	13	♂	20/30	−3	short		51	58	69	64	45	83	tt″	80.5	11111
			20/40				51	58	68	65	44	81	t	45.5	
1-131a	20	♂	20/15	0	tall		64	83	94	87	69	93	t′	48.0	22222
			20/15				60	85	96	89	70	92	t	38.0	
1-131b	14	♂	20/15	0	aver.?		62	80	85	80	60	93	t	38.5	22222
			20/15				62	81	88	81	64	93	t	39.0	
1-136	11	♀	20/200	−6			52	63	69	66	51	79	t	41.5	13222
			20/200	−15			53	65	70	65	52	72	t	47.5	
1-137	9	♂	20/40				43	54	60	58	46	73	t	39.5	23222
			20/40				47	57	62	59	47	70	t	38.5	
1-151	24	♀	20/30	−3	148.5	139.8	46	65	71	68	52	75	t′	49.5	11211
			20/30				45	66	71	66	50	75	t′	55.5	
1-152	22	♀	20/25	−2	156.6	152.3	46	62	70	66	45	84	t	43.0	11121
			20/70				47	63	70	67	45	81	t′	56.0	
1-153	15	♂	20/20	0	153.1	155.2	49	68	77	73	51	92	0		21121
			20/20				52	70	80	73	54	91	t′	50.0	
1-154	15	♂	20/70	—	156.2	143.5	48	66	75	74	56	94	tt′	58.5	11111
			20/100				48	66	75	72	54	91	t″	69.0	
1-157	12	♀	20/70	−5			46	53	65	59	44	72	t″	69.0	11211
			20/30	−3	136.2?		51	55	66	59	44	73	t″	71.5	
1-158	10½	♂			128.7?		47	52	61	58	43	72	tt″	63.0	21121
							49	54	61	57	43	72	t	37.5	
1-159	5½	♂			106.7		41	50	58	53	40	66	tt″	62.0	21111
							45	48	57	53	39	67	t	49.5	
1-160a	4½	♀					37	50	58	53	43	63	t	50.0	23222
							37	51	56	54	42	62	t	54.0	
1-160b	3	♀											t′	62.0	23313
													t′t′	63.0	

TABLE 13.—*Cont.*

Pedigree Number	Age	Sex	Visual Acuity Without Glasses (except with c̄)	Fundi Seen With	Stature (cm)	Span (cm)	Finger Length (mm)					Palm Width (mm)	t-triradius	*atd* Angle (°)	Classification
							I	II	III	IV	V				
1-161	24	♀		−3	152.8		46	67	74	71	51	77	t′	53.0	11221
							49	66	74	70	53	81	t	39.5	
1-163	15	♂			163.0	162.5	57	71	80	75	54	93	tt′t′	45.5	31121
							60	70	79	74	53	92	t′	43.0	
1-164a	18	♀			152.0	153.0	50	66	74	68	51	82	t	41	31222
							49	65	75	75	51	81	t	41.0	
1-164b	17	♂			168.0	174.5	61	76	83	75	58	94	t	38.0	32222
							58	80	86	77	60	94	t	40.5	
1-164c	9½	♀			129.0	124.5	49	59	67	61	49	73	t	46.0	32222
							47	56	64	58	45	71	t	44	
1-165b	12⅓	♂	20/40		129.0	126.0	49	57	65	61	44	83	t″	74.0	11111
			20/70				54	59	64	61	45	81	t″	77.0	
1-165d	5	♂			very		30	43	50	46	33	68	t′	60.0	21111
					short		33	46	51	47	34	65	t′	59.0	
1-168	25	♀	20/25c̄	0	159.0	155.5	49	65	73	68	48	91	tt′	49.0	22121
			20/25c̄				50	65	74	68	51	89	t	43.0	
1-169	19	♀			163.9	162.5	50	65	76	70	53	85	t′	41.5	22222
							51	66	76	71	50	85	t′	46.5	
1-185	11	♂	20/20	0	133.3?		39	52	61	55	40	72	t	43.5	21121
			20/20				40	53	59	54	37	70	t	42.0	
1-186a	10	♂					46	57	67	61	44	74			23232
							51	60	67	61	47	74			
1-188	5½	♂	20/25	−1	105.9	103.2							t	47	11311
			20/20										tt′	61.5	
1-191	9	♀	20/50c̄	+6	123.1		40	54	58	54	39	68	t	43	21121
			20/60c̄				40	52	58	52	38	65	t	43.5	
1-192	8	♂	20/100c̄		121.8	118.3	38	52	57	54	41	70	t	44.0	21121
			20/40c̄				40	50	55	51	36	70	t	43.5	
1-193	4⅓	♀	20/30c̄		103.7		35	46	52	48	31	60	t′	42.5	22122
			20/20c̄				34	47	52	48	33	58	t′	45.5	
2-9	76	♂	10′		159.0	159.0	60	75	85	79	60	95	t	42.0	21222
			10′				59	67	82	76	56	92	t	40.0	
2-12	58	♂	L.P.		166.5	168.5	56	70	79	72	57	87	tt′	50	21222
			no L.P.				61	69	80	73	56	88	t	39	
2-15	54	♀	20/50		138.8	139.5	50	60	72	69	55	87	t	40.5	21121
			20/25				50	62	71	66	52	81	t	41.5	
2-16	51	♀	20/20	0	159.3	151.3	47	67	74	70	51	82	t	44.0	22222
			20/20				50	66	73	68	53	82	t	43.5	
2-17	48	♂	20/20	0	161.2	172.0	66	74	87	84	63	97	t	38.0	21222
			20/20				61	73	85	83	64	97	t	43.0	
2-18	46	♀	20/20	0	155.5	157.3	57	71	79	73	56	89	t′	48.5	21211
			20/20				58	72	78	71	55	87	t′	59.5	
2-19	40	♂			155.0	151.5	48	70	81	73	56	96	t′	57.0	11114
							51	72	80	73	56	94	t′	62.0	
2-20	51	♀	20/40		156.5	154.0							t	44.5	21322
			20/30										t	43.5	
2-23	28	♀	20/25	−1	152.2	153.5	51	64	74	68	56	80	t	37.5	11221
			20/40				51	62	74	68	55	80	t	46.5	
2-27	3⅓	♂	20/30	0	92.6	91.5							t′	50.5	21311
			20/20										t′	72	

TABLE 14.—REPORTED INFORMATION ABOUT RELATIVES OF INDIVIDUALS WITH THE SPHEROPHAKIA-BRACHYMORPHIA SYNDROME WHO WERE NOT AVAILABLE OR WHO WERE TOO YOUNG FOR COMPLETE EXAMINATION

* Indicates age at death. In column under "Possible Classification" the first four digits refer respectively to eye, stature, finger-palm index and *atd* angle. In each of these the status of the stigma is identified by numerals as follows: 1, stigma present; 2, stigma absent; 3, undetermined. The fifth digits indicate: 1—heterozygote, 2—homozygous normal, 3—undetermined, and 4—homozygous affected.

Pedigree No.	Age	Sex	Possible Classification	Remarks
1-9a	45*	♂	33133	
1-10	77*	♀	31131	Schizophrenia
1-11	d	♀	31331	
1-12	85*	♀	31131	
1-14	d	♀	31131	Peculiar walk
1-15	d	♂	32332	
1-16	90	♀	32222	t, t; schizoid
1-19	86*	♂	32332	
1-22	d	♀	33333	Blind
1-23	54*	♂	33331	Schizophrenia
1-25	70*	♂	31131	
1-26	76	♂	21131	O.U. 20/40s, early cataracts, glaucoma? t′, t′
1-27	70	♀	32333	
1-28	72	♀	31131	Blind
1-29	68	♂	21222	O.D. 20/20, O.S. 20/30; t, t
1-30	76	♀	32233	Long palms
1-35	67*	♂	32331	
1-36	60*	♀	32332	
1-37	60*	♂	31331	
1-39	d	♂	33131	
1-41	62*	♂	31131	Peculiar walk
1-42	52*	♀	31231	
1-47	50?	♂	32231	Schizophrenia
1-48	46	♂	32233	
1-50	72*	♂	32233	Long palms
1-51	70	♀	32332	
1-54	69	♂	21121	O.U. 20/200s; O.D. aphakia; O.S. mature cataract; t, t
1-59	47	♂	21111	t′, t″
1-64	32	♂	31121	t, t
1-65				Of 6 sibs 2 are 31133 and 4 are 33333
1-87	d	♀	31131	
1-90	47	♀	31233	
1-91	57	♂	31131	
1-95	43	♂	33333	
1-97	2*	♂	33134	Extreme brachydactyly
1-98	39	♂	33333	
1-101	7*	♂	33333	
1-103	39	♀	33333	
1-108a	32	♀	32233	
1-108b	30	♂	31223	

TABLE 14.—*Cont.*

Pedigree No.	Age	Sex	Possible Classification	Remarks
1-138	6	♂	22222	O.D. 20/30$\bar{s}$; O.S. 20/20$\bar{s}$; t, t
1-140	38	♂	31131	
1-144	27	♂	22222	O.U. 20/15; t, t
1-148	34	♂	31231	
1-150a	1 da*	♀	33331	
1-150b	1 da*	♀	33331	
1-165a	14	♀	21131	O.U. 20/20
1-165c	10	♀	21131	O.U. 20/45
1-165e	3	♂	33331	
1-165f	1	♂	33331	
1-186b–g			33333	3 boys and 3 girls ages 1–8
1-189	3	♀	33333	
1-190	1	♂	33333	