

Genetics of Relative Toe Lengths¹

Arnold R. Kaplan

Data collected with the assistance of

Wilma Powell²

Two prerequisites for the use of a trait as a genetic marker are wide distribution and high penetrance. Relative toe length of the hallux or great toe compared to the adjacent or second toe is a normal anatomical trait featuring the above characteristics. An earlier study (Kaplan, 1963), based on family data derived from questionnaires completed by a group of 48 university students, advances the hypothesis of a simple Mendelian mode of genetic transmission involving two alleles and a single locus. The family reports in the previous study indicate that occurrence of a longer hallux, compared to length of the adjacent second toe, is based on a simple Mendelian factor recessive to the genotype for a longer second toe. The present report describes additional data which substantiate and extend the above hypothesis.

Subjects and methods

Our Cleveland Area Twin Registry has provided a sample of the population selected only on the basis of having a set of twins in the family. In addition to indicating the relative importance of genetic factors, twin data may be used as an economical substitute for a total population survey (Kallmann, 1953). In the present study, concordance-discordance rates are compared for the two twin categories. The twin data are also utilized for population frequency determinations of the two phenotypes. The latter determinations are made separately for the monozygotic and the dizygotic samples. Gene frequencies are then calculated from the phenotype frequencies, in accord with the given hypothesis.

Each subject, participating in other twin-family research programs at this laboratory and who was observed to have a second toe longer than the adjacent hallux, was requested to complete and return a pedigree questionnaire. These question-

¹ Supported by the State of Ohio, Department of Mental Hygiene and Correction, Division of Mental Hygiene; and supported by grants RG 9885 and HD 00581-02 from the National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare.

² Solicited and collected with the help of Edward V. Glanville, Diane Novak and Roberta P. Donaldson.

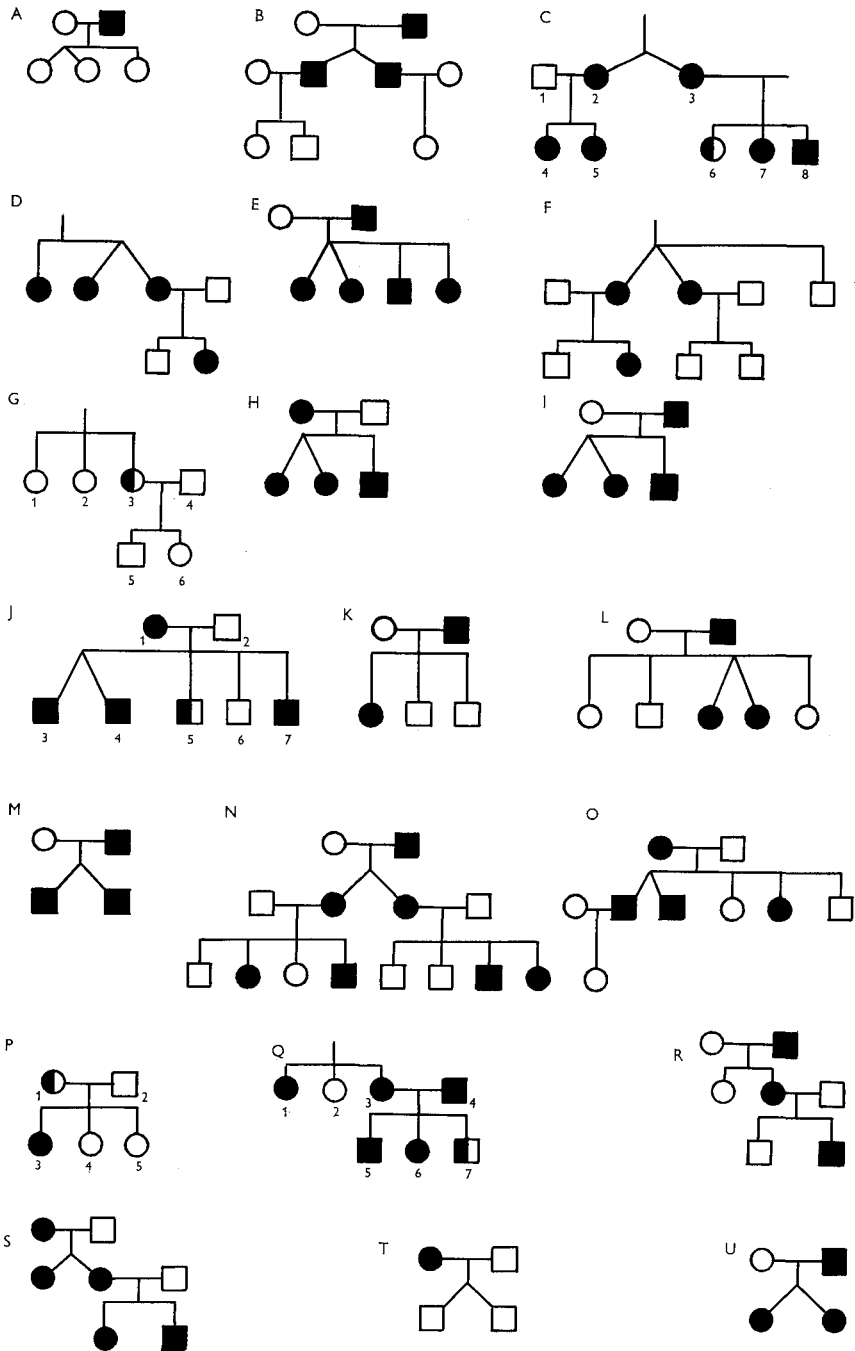


Fig. 1. Pedigree schematics

Full shadow indicates dominant trait bilaterally. Half shadow indicates dominant trait on one side only
 Monozygotic twins are indicated by joined branches

naires were submitted to 17 monozygotic and 12 dizygotic twin subjects, and to one non-twin. The pedigree forms returned (at the date of the present writing) include 16 of the 17 in the first group, four of the 12 in the second, and the one issued to a non-twin. Figure 1 indicates the 21 pedigrees, and Table 2 lists the numbers of individuals whose parents are discordant for the toe length trait. According to the above hypothesis, the genetic basis of the trait concerns one pair of alleles and a single locus, with the allele for 'longer hallux' being recessive to the one for 'longer second toe'. The apparent and expected distributions are compared in accordance with the calculated gene frequencies. The discordance and concordance rates are similarly examined for any significant deviation from the expected distribution. The possible effects of sex are also examined with a chi-square evaluation for the distribution of both traits (*i. e.*, 'longer hallux' and 'longer second toe') in the two sexes.

Data

Relative toe lengths have been determined for 214 twins, consisting of 63 monozygotic pairs and 44 dizygotic pairs. The individual twins are categorized according to whether the hallux or adjacent second toe is the longer of the two (Tab. 1). Subjects with a longer hallux on one foot and a longer (adjacent) second toe on the other foot are included in the category of 'subjects with longer second toe.'

Tab. 1. Distribution of twin subjects according to relative length of hallux and adjacent second toe

	Subjects with longer hallux	Subjects with longer second toe	Total individuals
Monozygotic twins	96	30	126
Dizygotic twins	67	21	88

Tab. 2. Offspring of discordant matings, as indicated in Fig. 1 according to trait and sex

	Subjects with longer hallux	Subjects with longer second toe	Total
Males observed	16	13	29
(Males expected)	(13.8)	(15.2)	(29)
Females observed	13	19	32
(Females expected)	(15.2)	(16.8)	(32)
Total observed	29	32	61
(Total expected)	(28.3)	(32.6)	(61)

Pedigree data have been obtained and are schematized (Fig. 1) for 21 families, each containing at least one member with a relatively long second toe compared to the length of the adjacent hallux. Five subjects (*C6*, *G3*, *J5*, *P1*, *Q7*) manifest bilateral discordance for the trait: the hallux is longer than the adjacent second toe on one foot, and the reverse situation occurs on the other foot. In each of the above five cases, the right foot is the one in which the second toe is longer than the hallux. One of the pedigrees (*P*) involves a bilaterally discordant parent mated to a homozygous recessive parent (according to the hypothesis advanced); and their offspring include one subject (*P3*) who manifests bilaterally the trait of a relatively long second toe.

Calculations and results

The 63 pairs of monozygotic twins manifest 100% concordance with respect to relative length of the hallux and adjacent second toe. The 44 pairs of dizygotic twins include 33 pairs or 75% of the dizygotic twin sample which are concordant for the trait, and 11 pairs or 25% of the sample which are discordant (Tab. 3).

Tab. 3. Distribution of monozygotic and dizygotic twin pairs according to concordance or discordance for the relative toe trait

	Concordant pairs	Discordant pairs	Total
Monozygotic twins observed and expected	63	0	63
Dizygotic twins observed	33	11	44
Dizygotic twins expected	36	8	44

According to the theory that the trait involves two alleles and a single locus, with the allele for longer second toe dominant to the one for longer hallux, subjects with a longer hallux are homozygous for the recessive allele. The genotypes may be schematized as *tt* for subjects with a longer hallux on each foot, *Tt* and *TT* for those with a longer second toe. Treating the monozygotic and dizygotic twin samples as two separate population surveys of the Caucasian population in the greater Cleveland area, the proportions of homozygous recessive subjects are:

$96/126 = 0.762$ for the monozygotic twins, and $67/88 = 0.761$ for the dizygotic twins. Gene frequency calculations according to the Hardy-Weinberg rule (Stern, 1960) yield identical values for each of the two twin populations:

$$p + q = (t) + (T) = p^2 + 2pq + q^2 = (tt) + (Tt) + (TT) = 1.00.$$

For the monozygotic twins:

$$p = (t) = (0.762)^{1/2} = 0.87.$$

For the dizygotic twins:

$$p = (t) = (0.761)^{1/2} = 0.87.$$

In each case:

$$q = (T) = 1.00 - p = 1.00 - 0.87 = 0.13.$$

The gene frequencies in each twin sample are 0.87 for the recessive allele (t) and 0.13 for the dominant allele (T). These derived figures for gene distributions are employed in determining the expected population frequencies of homozygous recessive (tt), homozygous dominant (TT), and heterozygous (Tt) individuals:

$$\begin{aligned} (tt) &= p^2 = (0.87)(0.87) = 0.757. \\ (Tt) &= 2pq = 2(.87)(.13) = 0.226. \\ (TT) &= q^2 = (0.13)(0.13) = 0.017. \\ p^2 + 2pq + q^2 &= 1.000 = 0.757 + 0.226 + 0.017. \end{aligned}$$

Table 2 is based on all individuals whose pedigrees (Fig. 1) indicate that they are the offspring of discordant matings (*i. e.*, parents are $tt \times T-$): one parent manifests the recessive trait and is homozygous for the recessive allele (tt) while the other parent manifests the dominant trait and is either heterozygous (Tt) or homozygous for the dominant allele (TT). The mixed matings produced 61 conceptions — *i. e.*, counting each pair of monozygotic twins as a single conception. The 61 include 29 genotypes which manifest the recessive phenotype and they are therefore homozygous for the recessive allele. The other 32 conceptions involve genotypes which manifest the dominant phenotype and they are therefore heterozygous for the particular locus (because one of the parents is homozygous for the recessive allele). The proportion of conceptions derived from mixed parental phenotypes (*i. e.*, one recessive parent and one dominant) expected to have one parent homozygous for the recessive allele and one homozygous for the dominant allele, is derived from the calculated (above) gene frequencies:

$$(TT) / (Tt) + (TT) = (q^2) / (2pq) + (q^2) = (0.017) / (0.226) + (0.017) = 17/243.$$

All conceptions from such mixed matings involve the heterozygous genotype which manifests the dominant phenotype. The proportion of conceptions derived from mixed matings which include one parent who is homozygous for the recessive allele and one who is heterozygous is similarly derived from the gene frequencies:

$$(Tt) / (Tt) + (TT) = (2pq) / (2pq) + (q^2) = (0.226) / (0.226) + (0.017) = 226/243.$$

The offspring from such matings are expected to be equally divided between homozygous recessive and heterozygous individuals and to include in each of the two genotypic categories:

$$(1/2)(226/243) = 113/243.$$

The 61 conceptions of the indicated mixed matings, according to the hypothesis and calculated gene frequencies, are expected to include individuals who are homozygous for the recessive allele:

$$(113/243) (61) = 28.3.$$

Similarly, the group is expected to include individuals who are heterozygous for the particular locus:

$$(113/243) (61) + (17/243) (61) = 28.3 + 4.3 = 32.6.$$

The observed numbers of individuals in the respective categories are 29 and 32. The deviations between observed and expected numbers (Tab. 2) of conceptions manifesting the two phenotypes yield the following chi-square value:

$$(0.7)^2 / (28.3) + (0.6)^2 / (32.6).$$

This indicates an insignificant probability (P) value for statistical significance.

An additional test of the genetic hypothesis involves comparisons of observed and expected number of concordant and discordant dizygotic twin pairs (Tab. 3). According to expected frequencies of the various parental pairs in the general population, the proportion of dizygotic twins expected to be concordant is: $(p^2)(p^2) + (p^2)(q^2)(2) + (q^2)(q^2) + (2pq)(q^2)(2) + (p^2)(2pq)(1/2)(2) + (2pq)(2pq)(p^2)(q^2)(2) + (q^2)(q^2) + (2pq)(q^2)(2) + (p^2)(2pq)(1/2)(2) + (2pq)(2pq)(5/8)$. The proportion of expected discordant pairs is: $(p^2)(2pq)(1/2)(2) + (2pq)(2pq)(3/8)$. In accordance with the calculated gene frequencies (*i. e.*, $p = 0.87$ and $q = 0.13$), the sample of 44 dizygotic twin pairs is expected to include $(44)(0.814) = 36$ concordant pairs, and $(44)(0.186) = 8$ discordant pairs. The chi-square value, based on observed and expected numbers (Tab. 3) therefore $= (3)^2 / 36 + (2)^2 / 8 = 0.75$, which yields a probability (P) value which is not statistically significant.

The possible influence of sex on the distribution of the two phenotypes is examined for the offspring of $tt \times T$ —parents (Tab. 2). The proportion of males in the sample is 29/61 and the proportion of females is 32/61. The observed and expected numbers of males with a longer hallux are, respectively, 16 and $(29/61)(29) = 13.8$. The observed and expected numbers of males with longer second toes are, respectively, 13 and $(32/61)(29) = 15.2$. The observed and expected numbers of females with a longer hallux are, respectively, 13 and $(29/61)(32) = 15.2$. The observed and expected numbers of females with longer second toes are, respectively, 19 and $(32/61)(32) = 16.8$. The chi-square value derived from the figures for observed and expected numbers in the two phenotypic categories for the two sexes is:

$$(2.2)^2 / 13.8 + (2.2)^2 / 15.2 + (2.2)^2 / 15.2 + (2.2)^2 / 16.8 = 1.28.$$

The probability (P) is not statistically significant.

Discussion

The present report describes studies on the genetics of relative length of the hallux and adjacent second toe. Relative toe lengths have been determined for twin subjects participating in our twin-family research programs. Zygosity diagnoses have been confirmed with various morphological characters (pigmentation of eyes, skin and hair, hair distribution patterns, shape of nose and mouth), dermatoglyphics, blood types³, taste thresholds (Kaplan, et al., 1963). Concordance-discordance comparisons for the toe length trait in the two twin categories (Tab. 3) indicate that the phenotypes have a primarily genetic basis. The 63 pairs of monozygotic twins manifest 100% concordance, compared to 75% concordance in 44 pairs of same-sex dizygotic twins. The data indicate that the relative length of hallux and adjacent toe may be utilized in zygosity diagnoses in conjunction with blood types and other normal morphological and biochemical traits.

Twins and other subjects who were observed to have a second toe longer than the adjacent hallux were requested to provide information concerning the familial distribution of the trait. The 21 pedigrees (Fig. 1) indicate distributions of the phenotypes which are entirely consistent with the hypothesis that the variable involves two alleles and a single genetic locus, the gene for relatively long hallux being recessive to the one for relatively long second toe. These data are consistent with earlier family data derived from 48 correspondents (Kaplan, 1963).

Five of the pedigrees considered in the present report — *C*, *G*, *J*, *P*, and *Q* — include subjects whose relative lengths of hallux and second toe are bilaterally discordant. One of the pedigrees, *P*, indicates that such an individual may transmit the bilaterally concordant trait to his offspring. Evidently, the dominant gene (*i. e.*, *T*, the gene for relatively long second toe compared to hallux) manifests variable expressivity. In most instances, the genetic factor is manifest bilaterally. A minority of individuals with the heterozygous genotype, however, indicate the dominant allele's manifestation only on one side. The present data are insufficient to prove whether or not such bilateral discordance may also be manifest in subjects with the homozygous dominant genotype. In each observed bilaterally discordant subject, the right foot manifests the dominant genotype. This phenomenon may be related to the report that observed size differences in brain hemispheres always involve a larger left hemisphere (Kaplan, 1960). Marked lateral neuromuscular dominance, when it occurs, involves the right side of the body and the left brain hemisphere (Bauer and Wepman, 1955). The present morphological observations are consistent with the hypothesis of a generalized ontogenetic predisposition to left cerebral and right somatic lateral dominance which interacts with the various specific genes (Kaplan, 1960). The bilateral morphological discordance, with right somatic penetrance

³ Blood typing carried out under the direction of Roger Marsters, Cleveland Metropolitan General Hospital and Western Reserve University School of Medicine.

slightly exceeding left somatic penetrance, is apparently a manifestation of the dominant genotype's variable expressivity.

The twin data are used as population surveys for the greater Cleveland area Caucasian population. Each of the twin categories, monozygotic and dizygotic, yields similar phenotype frequencies: 76% recessive (*i. e.*, longer hallux) and 24% dominant (*i. e.*, longer second toe). The identical distributions observed in the two sets of data substantiate each-other as accurate surveys of the population involved. The calculated gene frequencies, based on the phenotype frequencies, are 0.87 for the recessive allele (*t*) and 0.13 for the dominant allele (*T*). The genotypic distribution according to these figures consists of 0.757 homozygous recessive (*tt*), 0.226 heterozygous (*Tt*), and 0.017 homozygous dominant (*TT*). The genetic hypothesis and calculated gene frequencies, based on phenotype distributions in the twin subjects, are tested by comparing observed and expected numbers of offspring from the mixed parental pairs (*i. e.*, one parent of dominant phenotype and the other of recessive phenotype) indicated in Figure 1. The data (Tab. 2) demonstrate no significant deviation. Observed frequencies of concordant and discordant dizygotic twins are similarly tested, and the data indicate no significant deviation from expected frequencies (according to gene frequencies calculated from the twin phenotype distributions). The data are thus entirely consistent with the given hypothesis. There is no evidence for any influence of sex upon the trait's distribution or penetrance, according to statistical comparison of the observed and expected numbers of subjects of each sex in each category (Tab. 2).

Summary

Twin and pedigree data are presented which indicate that relative length of hallux and adjacent second toe is based on simple Mendelian genetic factors. The normal anatomical trait involves two alleles and a single autosomal locus. The factor for relatively long hallux is recessive to the one for relatively long second toe. There is no evidence of sex influence. Penetrance is 100%. Expressivity is variable, and bilateral discordance is observed in a minority of heterozygous subjects. In every such case, the dominant genotype is expressed in the right foot. The recessive and dominant phenotypes occur, respectively, in 76% and 24% of the greater Cleveland area Caucasian population. Gene frequencies in this population are 87% and 13%, respectively, for the recessive and dominant allele.

Acknowledgements

Gratitude is hereby expressed to the many twin-family subjects who have generously cooperated with our research projects. Particular thanks are due to Dr. Edward N. Hinko, former superintendant of the Cleveland Psychiatric Institute, whose cooperation and active facilitation of our basic research endeavors made the present study possible.

References

- BAUER R. W. and WEPMAN J. M.: Lateralization of cerebral functions. *J. Speech Hear. Dis.*, 1955, 20, 171-177.
- KALLMANN F. J.: Heredity in health and mental disorder, Principles of psychiatric genetics in the light of comparative twin studies, 1953, pp. 67-68. New York: W. W. Norton & Co., Inc.
- KAPLAN A. R.: A theory on the biology of lateral dominance. *A. Ge. Me. Ge.*, 1960, 9, 318-324.
- Inheritance of relative digit size in the human foot. *J. Hered.*, 1963, 54, 35-37.
- POWELL W., FISHER R. and MARSTERS R.: Reexamination of genetic aspects of taste thresholds for thiourea-type compounds. *Proc. XI Int. Cong. Genetics*, The Hague, The Netherlands, September 1963. Abstract in S. J. Geerts (ed.), *Genetics today*, v. 1, 292-293, Pergamon Press, London, 1963.
- STERN C.: Principles of human genetics, Second Edition, 1960, pp. 149-173. San Francisco: W. H. Freeman & Co.

RIASSUNTO

Vengono presentati dati gemellari e genealogici indicanti che la lunghezza relativa dell'alluce e del dito ad esso adiacente si basa su fattori genetici mendeliani semplici. Il carattere anatomico normale comporta due alleli ed un solo locus autosomico. Il fattore per la lunghezza relativa dell'alluce è recessivo rispetto a quello per la lunghezza relativa del secondo dito. Non vi sono prove di influenza da parte del sesso; la penetranza è del 100%; l'espressività è variabile ed una discordanza bilaterale può essere riscontrata in una minoranza di individui eterozigotici. In ogni caso del genere, il genotipo dominante si esprime nel piede destro. I fenotipi recessivo e dominante compaiono rispettivamente nel 76% e nel 24% della popolazione caucasica della zona maggiore di Cleveland. Le frequenze geniche della popolazione sono dell'87%, per l'allele recessivo e del 13%, per quello dominante.

RÉSUMÉ

L'A. présente des données sur des jumeaux et arbres généalogiques, d'après lesquelles la longueur relative du gros orteil et de l'orteil adjacent se baseraient sur des facteurs génétiques mendéliens simples. Le trait anatomique normal emporte deux allèles et un seul locus autosomique. Le facteur pour la longueur relative du gros orteil est récessif par rapport à celui pour la longueur relative du deuxième orteil. Le sexe ne paraît exercer aucune influence; la pénétrance est de 100%; l'expressivité est variable et une discordanche bilatérale peut être remarquée chez une minorité d'individus hétérozygotiques. Dans tous ces cas le génotype dominant s'exprime dans le pied droit. Les phénotypes récessif et dominant paraissent respectivement dans 76% et 24% de la population caucasienne de la zone principale de Cleveland. Les fréquences géniques de la population sont de 87% pour l'allèle récessif et de 13% pour l'allèle dominant.

ZUSAMMENFASSUNG

Es werden Zwillings- und Sippenerhebungen angeführt, aus denen hervorgeht, daß die relative Länge der großen und der zweiten Zehe auf einfachen mendelschen Erbfaktoren beruht. Das normale anatomische Merkmal hat zwei Allele und nur einen Autosomen-locus. Der Faktor für die relative Länge der großen Zehe ist gegenüber dem für die relative Länge der zweiten Zehe rezessiv. Für irgendwelche Einflüsse des Geschlechtes fehlen die Beweise. Die Penetranz beträgt 100%. Die Expressivität ist

verschieden und bei einer Minderheit von Heterozygoten läßt sich eine Diskordanz zwischen den beiden Seiten finden. In jedem solchen Falle äußert sich der dominante Genotyp im rechten Fuß. Der rezessive und der dominante Phänotyp treten bei der kaukasischen Bevölkerung der größten-Zone von Cleveland im Verhältnis von 76% bzw. 24% auf. Die Gen-Frequenzen in der Bevölkerung betragen 87% für das rezessive und 13% für das dominante Allel.