Studies on Linkage Between Phenylketonuria and the Blood Groups[1]

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PENROSE AND OTHERS (Munro, Penrose, and Taylor, 1939, Penrose, 1945 and 1951) reported data which suggested that loose linkage between phenylketonuria and the ABO locus may exist. The data were too few to permit a statistically valid conclusion to be reached. The difficulty of accumulating the large samples necessary to test loose linkage for a recessive character rigorously, prevented these authors from bringing the analysis to a statistically significant conclusion.

In 1956 Hsia, Driscoll, Troll, and Knox reported that the heterozygous carriers for phenylketonuria can be detected by means of a phenylalanine tolerance test. A load of 0.1 gm. per kg. body weight of L-phenylalanine was administered by mouth, and samples of blood were taken at one, two, and four hours, and the plasma phenylalanine levels determined. It was found that the heterozygotes had plasma levels on the average twice that seen among normal controls and the difference between the two groups was highly significant. The ability to detect the heterozygote combined with newly reported methods for the detection of linkage in man (Morton, 1955) made it seem worth while to reinvestigate the problem.

The purpose of the present paper is to report on linkage relationships between the genes for phenylketonuria and those for the blood groups. The data have been subjected to sequential analysis with the phenylketonuric gene being treated both as a recessive and as an intermediate dominant, where the heterozygote is identified by means of the phenylalanine tolerance test.

MATERIALS AND METHODS

A total of 23 families located in New England and the Midwest were studied. In each instance, the diagnosis of phenylketonuria in the homozygote was confirmed by the presence of phenylpyruvic acid in the urine or the elevation of phenylalanine in the plasma, or both. With one exception, which has been reported in a separate communication (Hsia, Knox, and Paine, 1957), all of the homozygotes were mentally deficient.

Venous blood samples were tested for the following blood groups: (1) ABO (2) MNS (3) Rh (4) P (5) K and (6) Fy.

Available relatives (as shown in Appendix Table A) were subjected to a stand-

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ard phenylalanine tolerance test (Hsia et al., 1956). One-tenth of a gram per kg. of L-phenylalanine (obtained from Nutritional Biochemicals, Cleveland, Ohio) in crystalline form was mixed with fruit juice and given by mouth after an overnight fast. Samples of plasma were taken one and two hours after the load and the phenylalanine level determined by the phenylethylamine method of Udenfriend and Cooper (1953) as modified by Hsia, Knox, Quinn, and Paine (1957). The plasma phenylalanine levels at one and two hours were summed and used to establish the discriminant between heterozygotes and normal controls.

The tolerance test to detect heterozygotes for phenylketonuria (Hsia et al., 1956) is not completely successful (Hsia, 1958). Regardless of the score used (phenylalanine-tyrosin ratio, the sum of the one- and two-hour phenylalanine levels, etc.) there is considerable overlap of the scores for known heterozygotes and presumed homozygous normals. An example of this is shown in Fig. 1, where the logarithms of the sums of the one- and two-hour phenylalanine levels in mgms % for 48 heterozygotes (parents of affected children) and 38 presumed normals are plotted. (Unpublished calculations showed that for our data this score was as satisfactory as any other for discriminating between homozygotes and heterozygotes.) We were confronted with the alternatives of treating phenylketonuria as a complete recessive, or of using some arbitrary criteria for deciding whether an individual was homozygous or heterozygous. We decided to utilize both alternatives.

The heterozygosity of a nonphenylketonuric member of a family was determined as follows: 1. Normal curves were fitted to the distributions of the

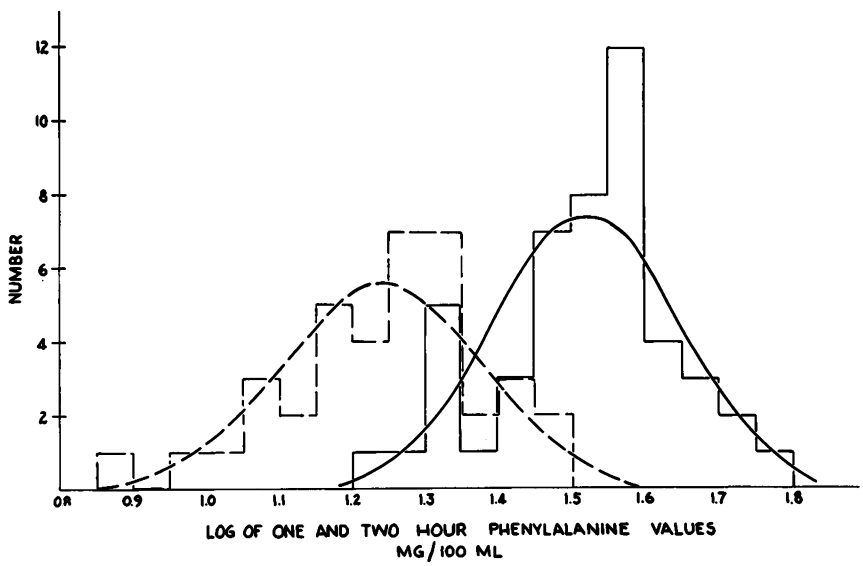

FIG. 1. Histograms and fitted normal curves for the distribution of the sums of the one- and two-hour phenylalanine levels in 38 normal adults (dashed lines) and 48 heterozygotes (solid lines).

logarithms of the sum of the one- and two-hour phenylalanine levels for known heterozygotes and for presumed normals. 2. When it was ascertained that the fitted normal curves were satisfactory representations of these distributions, deviations from the means were computed, taking into account the prior odds (segregation ratios), so that the frequency, at these deviations, of homozygous normals would be to that of heterozygotes as 4:1 or as 1:4. Values falling at or to the left of the former point were considered to be for homozygous normals; those at or to the right of the latter point were considered to be for heterozygotes. Values falling between these points were classified as indeterminate and not used for linkage analyses. By this procedure the odds were at least 4:1 that the classification of each individual was correct.

The decision points were determined by equating the ratio of the ordinate of the normal curve fitted to the distribution of the sum of the one and two hour plasma phenylalanine levels of the homozygotes, to the ordinate fitted to that of the heterozygotes, at 4 for the upper limits for normals and at 0.25 for the lower limit for heterozygotes, and solving for the value of the sum of the one and two hour levels which would satisfy these values of the equation.

The equation is:

$$\frac{y_1}{y_2} = \frac{\frac{N_1}{\sigma_1\sqrt{2\pi}} \exp - \frac{(x_i - \bar{X}_1)^2}{2\sigma_1^2}}{\frac{N_2}{\sigma_2\sqrt{2\pi}} \exp - \frac{(x_i - \bar{X}_2)^2}{2\sigma_2^2}} = Y$$

where y_i = ordinate of normal curve

N_1 = the *a priori* frequency of homozygous normals relative to that of heterozygotes

N_2 = the *a priori* frequency of heterozygotes relative to that of homozygous normals

x_i = logarithm of the sum of the one- and two-hour phenylalanine levels at a decision point

$\bar{X}$ = mean

σ = standard deviation

The subscripts refer to homozygous normals (1) and to heterozygotes (2).

The relative frequencies of homozygotes and heterozygotes are 1:1 for matings of Phph × PhPh and 1:2 for matings of Phph × Phph. Using the values and the computed means and standard deviations, the following "cut-off" points in mgms % for the sum of the one- and two-hour phenylalanine levels were established:

Mating	x_i at Y of Indicated Value	
	Y = 4	Y = 0.25
1. Phph × PhPh	20.3	29.1
2. Phph × Phph	18.5	25.9

Thus for cross 1 all those whose scores were 20.3 mgms % or lower were con-

sidered homozygous normal; those whose scores were 29.1 mgms % or higher were considered heterozygous; all others were excluded from consideration. Similarly, for cross 2 all those whose scores were 18.5 mgms % or lower were considered homozygous normal; those whose scores were 25.9 mgms % or higher were considered heterozygous; all others were excluded from consideration.

The family data upon which the linkage caculations are based are presented in Appendix Table A. Since only two of the parents and one of the siblings tested had weights exceeding 90 kilograms, the heights and weights of the individuals are not recorded in the table, nor were they considered in determining heterozygotes (Renwick, Lawler, and Cowie, 1960).

Scores for the sequential test for linkage (Morton, 1955) were computed for the ABO, MNS, Rh, Fy, K, and P loci, treating phenylketonuria as an intermediate dominant and as a recessive. We have in addition computed the linkage scores for the MN, and Rh loci for the families reported by Munroe (1947) and by Penrose (1951), treating phenylketonuria as a recessive. The totals for the scores are presented in Tables 1 and 2. Renwick et al. (1960) have examined the ABO data in detail.

When phenylketonuria is treated as an intermediate dominant (Table 1), the following conclusions may be drawn: ABO: linkage of .1 or less is excluded and probably also linkage of .2; MNS and Rh: linkage of .1 or less is excluded; K: linkage of .05 or less is excluded. No conclusions may be drawn concerning looser linkages than those mentioned above for these loci, nor for any linkage (except absolute linkage which is excluded) concerning the Fy and P loci.

TABLE 1. SEQUENTIAL ANALYSIS SCORES FOR LINKAGE BETWEEN PHENYLKETONURIA AND VARIOUS BLOOD GROUP LOCI. PHENYLKETONURIA TREATED AS AN INTERMEDIATE DOMINANT[1]

Blood Groups	No. of Families	z at Specified Values of θ				
		.05	.10	.20	.30	.40
ABO	12	−7.6839[2]	−4.5465	−1.9450	−.7061	−.0455
MNS	15	−7.0652[3]	−3.8228	−1.1862	−.2749	+.1717
Rh	16	−6.2933	−3.3098	− .9829	−.1651	−.0650
Fy	4	− .6807[4]	− .5104	− .1038	+.0074	+.0361
K	5	−2.3537	−1.3516	− .5307	−.1908	−.0424
P	5	− .1912	− .0112	+ .0666	+.0476	+.0144

[1] Based on determination of the heterozygote by means of the phenylalanine stress test. Those for whom the *a priori* expectation of heterozygosity was ½ and for whom the sum of the 1- and 2-hour plasma phenylalanine levels was less than 20.3 mgm/100 ml., were considered homozygous normal; if the sum exceeded 29.1 mgm/100 ml., they were considered heterozygotes. All others were excluded from consideration. Those for whom the *a priori* expectation of heterozygosity was ⅔ were considered homozygous normal if the sum of the 1- and 2-hour readings was less than 18.5 mgm/100 ml.; they were considered heterozygous if the sum exceeded 25.9 mgm/100 ml. All others were excluded from consideration. Parents of affected children were accepted as heterozygotes regardless of their scores.

[2] Based on 11 families.

[3] Based in 12 families.

[4] Based on 3 families.

TABLE 2. SEQUENTIAL ANALYSIS SCORES FOR LINKAGE BETWEEN PHENYLKETONURIA AND VARIOUS BLOOD GROUP LOCI. PHENYLKETONURIA TREATED AS A RECESSIVE

Blood Groups	Source	No. of Families	z at Specified Values of θ				
			.05	.10	.20	.30	.40
ABO	This study	14	−1.9539	−1.0060	−.3065	−.0803	−.0128
MNS	This study	18	−3.8833[1]	−2.0976	−.7709	−.2607	−.0536
	Munro (1947)	16	—	−1.1207	−.0844	+.1076	+.0505
	Penrose (1951)	2	—	+.0793	+.0540	+.0275	+.0075
	The 3 studies	36	−3.8833[1]	−3.1390	−.8013	−.1256	−.1212
Rh	This study	19	−1.9938[2]	−1.7446	−.6425	−.2133	−.0436
	Penrose (1951)	5	−.8744	−.5294	−.2098	−.0723	−.0152
	The 2 studies	24	−2.8682	−2.2740	−.8523	−.2856	−.0588
Fy	This study	5	−.5845	−.1856	+.0370	+.0509	+.0178
K	This study	4	−.5181	−.2712	−.0834	−.0213	−.0032
P	This study	4	+.5147	+.4198	+.2498	+.1162	+.0300

[1] Based on 17 families.
[2] Based on 14 families.

Similar conclusions may be drawn from the data derived when phenylketonuria is treated as a recessive, except that the amount of information for each locus is less. The latter observation indicates that few if any errors were made in classifying heterozygotes on the basis of the stress test and the derived "cut-off" points.

It is perhaps worth noting that the scores for the P locus are suggestive of linkage. None of the scores are significant, but only 5 families were available for analysis with phenylketonuria treated as an intermediate dominant and 4 families with phenylketonuria treated as a recessive.

It is apparent that many more data are required to exclude loose linkage (.3 or .4). It is also apparent that such data can best be obtained by treating phenylketonuria as an intermediate dominant. Unfortunately, the available tests for detecting the heterozygote are relatively inefficient; hence, until they are improved, it would not seem desirable to pursue the linkage study.

SUMMARY

Linkage between phenylketonuria and the ABO, MNS, Rh, P, K, and Fy loci was examined by Morton's sequential method, treating phenylketonuria as an intermediate dominant and as a recessive.

Linkage with ABO, Rh, or MNS as close as .1 or less is excluded.

Linkage with K of .05 or less is excluded.

The data are insufficient to permit other conclusions.

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TABLE A. FAMILY DATA

In each family the father is listed first, followed by the mother and their children.

Fam.	No. in Ped.	Sex	Year of Birth	Sum of 1 and 2 hour phenyl-alanine levels in mgms %	Genotype	A	B	M	N	S	C	D	E	c	e	Fy[a]	K	P
1-P6	I-1	M	12	34.7	Phph	+	−	+	−	−	−	−	−	+	n	+	−	−
	2	F	11	38.0	Phph	−	−	+	−	+	+	+	−	+	n	+	+	−
	II-1	M	38	25.2	Ph?	+	−	+	−	+	−	+	−	+	n	+	+	−
	2	F	41	—	phph	+	−	+	−	+	+	+	−	+	n	+	+	−
	3	F	43	—	phph	−	−	+	−	+	−	+	−	+	n	+	−	−
2-P7	I-1	M	30	41.3	Phph	−	−	+	+	+	+	+	−	+	n	+	−	+
	2	F	29	39.8	Phph	+	−	+	+	−	−	−	−	+	n	+	−	+
	II-1	M	52	—	phph	+	−	+	+	+	+	+	−	+	n	+	−	+
	2	F	54	n	Ph?	+	−	+	+	−	−	−	−	+	n	+	−	+
	3	F	55	—	phph	−	−	−	+	−	−	−	−	+	n	−	−	+
	4	M	57	n	Ph?	−	−	+	+	−	−	−	−	+	n	+	−	−
3-P8	I-1	M	16	30.9	Phph	−	−	+	+	−	+	+	−	+	n	−	−	+
	2	F	20	39.9	Phph	−	−	+	+	−	+	+	−	+	n	+	−	+
	II-1	F	41	31.0	Phph	−	−	+	+	−	−	−	−	+	n	+	−	+
	2	M	42	—	phph	−	−	+	+	n	−	−	−	+	n	−	−	+
	5	M	54	—	phph	−	−	+	+	−	+	+	−	+	n	−	−	+
4-P9	I-1	M	16	31.6	Phph	−	+	+	+	−	−	+	+	+	+	+	−	−
	2	F	26	36.9	Phph	−	−	+	−	+	−	+	+	+	+	−	−	+
	II-3	M	48	18.8	Ph?	−	−	+	−	−	−	−	−	+	n	−	−	+
	4	M	54	—	phph	−	+	+	+	+	−	−	−	+	n	+	−	−
5-P13	I-1	M	24	20.6	Phph	−	−	+	+	+	+	+	−	+	n	−	−	−
	2	F	22	17.6	Phph	−	+	+	+	+	+	+	−	+	n	+	−	−
	II-1	M	48	18.8	Ph?	−	+	+	+	+	+	+	−	+	n	+	−	−
	2	F	T 48	6.0	PhPh	−	+	+	−	+	+	+	−	−	n	+	−	−
	3	F	50	—	phph	−	+	+	+	−	+	+	−	+	n	+	n	−
6-P1	II-5	M	27	38.6	Phph	−	+	+	−	+	+	+	−	+	n	+	−	−
	6	F	28	30.0	Phph	−	−	+	+	+	−	−	−	+	n	−	−	−
	III-5	M	49	—	phph	−	+	+	+	+	+	+	−	+	n	+	−	−
	6	M	55	—	phph	−	−	+	−	+	+	+	−	+	n	−	−	−
7-P3	I-1	M	80	30.6	Phph	−	−	+	−	n	+	+	−	−	n	+	−	−
	2	F	82	19.1	PhPh	+	−	+	−	n	+	+	−	−	n	+	−	+
	II-1	M	12	13.2	PhPh	−	−	+	−	n	+	+	−	−	n	+	−	−
	2	M	14	28.9	Phph	+	−	+	−	−	+	+	−	−	n	+	−	−
	3	F	16	15.4	PhPh	−	−	+	−	n	+	+	−	−	n	+	−	+
	4	M	19	13.2	PhPh	+	−	+	−	n	+	+	−	−	n	+	−	+
8-P3	II-2[a]	M	14	28.9	Phph	+	−	+	−	−	+	+	−	−	n	+	−	−
	2[a]	F	17	33.7	Phph	−	−	+	+	+	+	+	−	+	n	+	+	+
	III-1	M	44	13.7	PhPh	−	−	+	+	−	+	+	−	−	n	+	+	−
	2	M	48	—	phph	+	−	+	+	−	+	+	−	−	n	+	n	−
	3	M	53	n	Ph?	+	−	+	−	+	+	+	−	+	n	+	−	+
	4	F	55	—	phph	+	−	+	+	−	+	+	−	−	n	+	−	−

TABLE A.—*Continued*

Fam.	No. in Ped.	Sex	Year of Birth	Sum of 1 and 2 hour phenyl-alanine levels in mgms %	Genotype	A	B	M	N	S	C	D	E	c	e	Fy^a	K	P
9-P5	I-1	M	06	30.1	Phph	−	+	+	+	+	+	+	−	−	n	+	−	−
	2	F	16	17.6	Phph	+	−	+	+	+	+	+	+	+	+	+	−	−
	II-1	F	43	24.2	Ph?	+	+	−	+	+	+	+	−	−	n	+	−	−
	2	M	46	—	phph	+	−	+	−	−	+	+	+	+	+	+	−	−
10-P11	I-1	M	24	40.2	Phph	−	−	+	−	+	+	+	−	−	n	−	−	+
	2	F	29	29.8	Phph	+	+	−	+	+	+	+	−	−	n	+	+[b]	+
	II-1	F	—	—	phph	n	n	n	n	n	n	n	n	n	n	n	n	n
	2	F	50	31.2	Phph	+	−	+	+	+	+	+	−	−	n	−	−	+
	3	M	52	20.8	Ph?	+	−	+	+	+	+	+	−	−	n	n	−	+
11-P10	I-1	M	12	34.3	Phph	+	−	+	+	−	+	+	−	+	n	+	−	+
	2	F	12	n	Phph	+	+	−	+	n	+	+	−	+	n	+	−	+
	II-2	M	49	15.5	PhPh	+	−	+	+	n	+	+	−	+	n	+	−	+
	3	M	51	—	phph	+	+	−	+	−	−	−	−	+	n	+	−	+
12-P2	I-1	M	79	39.2	Phph	+	−	+	−	n	+	+	−	−	n	+	−	+
	2	F	78	15.8	PhPh	−	−	+	+	n	+	+	−	+	n	−	+	+
	II-1	F	08	23.7	Ph?	+	−	+	+	n	+	+	−	+	n	−	−	+
	2	M	10	31.5	Phph	−	−	+	+	n	+	+	−	+	n	−	+	+
	3	M	13	29.7	Phph	−	−	+	−	+	+	+	−	−	n	−	+	−
	4	M	15	26.0	Ph?	−	−	+	−	n	+	+	−	−	n	−	−	+
	5	F	22	3.9	PhPh	−	−	+	+	n	+	+	−	+	n	−	+	n
	6	F	28	13.3	PhPh	−	−	+	−	n	+	+	−	−	n	+	−	+
13-P2	II-2	M[c]	10	31.5	Phph	−	−	+	+	n	+	+	−	+	n	−	+	+
	2a	F	—	n	PhPh[d]	−	−	+	−	+	+	+	−	+	n	+	−	−
	III-1	M	41	15.4	PhPh	−	−	+	−	+	−	−	−	+	n	−	+	−
	2	M	44	16.2	PhPh	−	−	+	−	+	−	−	−	+	n	+	+	−
14-P2	II-3	M[c]	13	29.7	Phph	−	−	+	−	+	+	+	−	−	n	−	+	−
	3a	F	15	28.9	Phph	−	−	−	+	−	+	+	−	+	n	−	−	−
	III-3	F	41	17.8	PhPh	−	−	+	+	+	+	+	−	−	n	−	+	−
	4	F	44	28.3	Phph	−	−	+	+	−	+	+	−	−	n	−	−	−
	5	F	46	—	phph	−	−	+	+	+	+	+	−	−	n	−	+	−
	6	F	52	—	phph	−	−	+	+	−	+	+	−	−	n	−	+	−
15-P2	II-4	M[c]	15	26.0	Ph?	−	−	+	−	n	+	+	−	−	n	−	−	+
	4a	F	—	n	PhPh[d]	−	−	+	−	+	+	+	−	−	n	+	−	−
	III-3	M	42	15.7	PhPh	−	−	+	−	+	+	+	−	−	n	−	−	+
	4	F	46	10.7	PhPh	−	−	+	−	−	+	+	−	−	n	+	−	−
16-P14	I-1	M	18	24.3	Phph	−	−	+	+	n	+	+	−	+	n	+	−	−
	2	F	20	18.2	Phph	+	−	+	+	n	−	−	+	+	+	+	−	−
	II-1	M	40	23.7	Ph?	−	−	+	+	n	+	+	−	+	n	+	−	−
	2	M	44	11.7	PhPh	+	−	+	−	n	+	+	−	+	n	+	−	−
	3	M	52	—	phph	+	−	+	−	n	+	+	+	+	+	+	−	−

TABLE A.—*Continued*

Fam.	No. in Ped.	Sex	Year of Birth	Sum of 1 and 2 hour phenyl-alanine levels in mgms %	Genotype	A	B	M	N	S	C	D	E	c	e	Fy[a]	K	P
17-P17	I-1	M	17	25.7	Phph	−	−	+	+	+	+	+	−	+	n	+	−	−
	2	F	20	20.7	Phph	−	+	+	−	+	+	+	−	+	n	+	−	−
	II-1	M	42	15.0	PhPh	−	+	+	+	+	+	+	−	+	n	+	−	−
	2	M	44	—	phph	−	+	+	−	+	+	+	−	−	n	+	n	−
18-P16	I-1	M	91	38.3	Phph	+	−	+	+	+	−	−	−	+	n	+	−	−
	2	F	96	52.8	Phph	−	−	+	+	−	−	−	−	+	n	+	−	−
	II-1	M	19	—	phph	+	−	+	+	−	−	−	−	+	n	n	−	−
	3	M	23	17.8	PhPh	−	−	+	+	−	−	−	−	+	n	+	−	−
	4	F	28	22.1	Ph?	+	−	+	−	+	−	−	−	+	n	+	−	−
	5	F	31	—	phph	+	−	+	+	+	−	−	−	+	n	n	−	−
20a-P18	I-3	M	07	44.5	Phph	−	−	+	−	+	+	+	−	+	n	−	−	−
	4	F	12	28.7	PhPh	+	−	−	+	+	+	+	+	+	+	+	−	+
	II-3	M	30	22.0	Phph	+	−	+	+	+	+	+	+	+	+	+	−	+
	5	F	51	24.6	Ph?	−	−	+	+	+	+	+	+	+	+	+	−	+
20b-P18	I-1	M	00	25.4	PhPh	+	−	−	+	−	−	−	−	+	n	+	−	+
	2	F	04	26.6	Phph	−	−	+	−	−	−	−	−	+	n	+	+	+
	II-1	F	29	19.9	Phph	+	−	+	+	−	−	−	−	+	n	+	−	+
	2	F	34	33.9	Phph	−	−	+	+	−	−	−	−	+	n	+	+	+
20c-P18	II-3	M[e]	30	22.0	Phph	+	−	+	+	+	+	+	+	+	+	+	−	+
	1	F[f]	29	19.9	Phph	+	−	+	+	−	−	−	−	+	n	+	−	+
	III-1	F	53	15.1	PhPh	+	−	−	+	+	+	+	−	+	n	+	−	+
	2	F	56	—	phph	+	−	+	+	−	+	+	−	+	n	+	−	+
21-P19	II-1	M	20	27.7	Phph	+	+	+	+	+	+	+	−	+	n	+	−	−
	2	F	24	16.0	Phph	+	−	+	+	−	+	+	−	−	n	+	−	+
	III-1	M	48	2.0	PhPh	+	−	+	+	−	+	+	−	−	n	+	−	+
	2	M	—	—	phph	+	−	−	+	−	+	+	−	−	n	+	−	−
21a-P19	I-1	M	88	26.7	Phph	−	−	+	−	−	+	+	−	−	n	+	−	+
	2	F	98	16.1	PhPh	+	−	−	+	−	+	+	−	+	n	−	−	+
	II-2	F[g]	24	16.0	Phph	+	−	+	+	−	+	+	−	−	n	+	−	+
	3	F	27	6.5	PhPh	+	−	+	+	−	+	+	−	−	n	+	−	+
22	I-1	M	28		Phph	−	+	+	+	+	+	+	+	+	+	+	−	+
	2	F	28		Phph	−	+	−	+	−	+	+	−	+	n	+	−	+
	II-2	F	51		Phph	−	−	+	+	+	−	+	+	+	+	+	−	+
	4	F	56		phph	−	+	−	+	−	+	+	−	+	n	−	−	+
26-P21	I-1	M	30	38.9	Phph	−	−	+	+	+	−	−	−	+	n	+	−	−
	2	F	35	19.9	Phph	+	−	−	+	−	+	+	−	+	n	+	−	−
	II-1	M	57	—	phph	+	−	−	+	−	+	+	−	+	n	+	−	−
	2	M	57	—	phph	+	−	+	+	+	+	+	−	+	n	+	−	−

TABLE A.—*Continued*

Fam.	No. in Ped.	Sex	Year of Birth	Sum of 1 and 2 hour phenyl-alanine levels in mgms %	Genotype	A	B	M	N	S	C	D	E	c	e	Fy[a]	K	P
27-P22	I-1	M	26	48.9	Phph	+	−	+	+	+	−	+	+	+	−	+	−	+
	2	F	31	55.7	Phph	−	−	+	−	+	+	+	−	+	n	+	−	+
	II-2	M	50	30.0	Phph	−	−	+	+	+	−	+	+	+	+	+	−	+
	3	M	52	—	phph	+	−	+	+	n	−	+	+	+	+	+	−	+
	4	F	53	51.0	Phph	−	−	+	−	+	−	+	+	+	+	+	−	+
	5	M	55	22.0	Ph?	+	−	+	−	+	−	+	+	+	+	+	−	+
	6	F	56	—	phph	+	−	+	−	+	+	+	+	+	+	+	−	+
	7	M	57	40.4	Phph	−	−	+	+	+	+	+	+	+	+	+	−	+
	8	M	58	—	phph	−	−	+	+	−	−	+	+	+	+	+	−	+

[a] His parents are I-1 and I-2 of 7-P3.
[b] Tested with k.
[c] His parents are I-1 and I-2 of 12-P2.
[d] Assumed.
[e] His parents are I-3 and I-4 of 20a-P18.
[f] Her parents are I-1 and I-2 of 20b-P18.
[g] Mother of Family 21-P19.