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Genetic effect of mottled locus on reproduction and preweaning growth in laboratory mice *

M. D. Erdman [1], F. A. Verley [2] and K. Bondari [3]

[1] USDA-ARS, Tifton, GA 31793, USA
[2] Department of Biology, Northern Michigan University, Marquette, MI 49855, USA
[3] Statistical and Computer Services, University of Georgia, Tifton, GA 31793, USA

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Summary. An experiment was conducted to study the maternal and fetal effects of the sex-linked gene tortoise on litter size, birth weight, body weight from birth to 30-day of age, and mortality in normal (N) and mutant (M) mice (*Mus musculus*). The experiment involved two mating types: (1) N×N (dam×sire) which produced normal male and normal female offspring and (2) M×N which produced mutant males that died in utero, mutant females and normal male and female offspring. Comparison 1 consisted of all phenotypically normal male and female offspring from both N×N and M×N mating types born in 2 parities. The data supports the hypothesis that the tortoise gene, when present in the dam, did not significantly affect the body weight of normal progeny prior to 18 days old. There is also evidence for a negative maternal effect of the tortoise gene on body weight from 21 to 30 days of age postpartum. Mating type×parity interaction was not significant prior to 9 day postpartum. Sex of mice did not influence body weight of siblings prior to 18 day old, but males were heavier than females thereafter. Normal and mutant females born in six parities from the M×N mating type constituted Comparison 2. The birth weight of the offspring in Comparison 2 was not significantly influenced by the presence of the tortoise gene. All other body weight measurements, however, were lower for mutant females when compared to normal females. Parity affected all body weight measurements in both comparisons. Mortality rate of the offspring was not influenced by parental mating type or parity, but sex differences were observed. Mutant females had higher mortality than normal sisters. This study provides evidence that the mottled locus in the tortoise dam and progeny influences growth and survival.

Key words: Laboratory mice – Menkes' kinky hair syndrome – Litter size – Sex-linked gene – Growth

Introduction

Menkes' Kinky Hair Syndrome (MKHS) in humans (Menkes et al. 1962; Danks et al. 1972; Danks 1983) and mottled mice are sex-linked, lethal disorders of copper metabolism (Hunt 1974; Danks 1977). Although the actual mechanism of the disorders is still unknown (Anonymous 1981, 1984), several studies provide evidence that impaired copper metabolism is involved (Evans and Reis 1978; Starcher et al. 1978; Prins and Van Den Hamer 1980, 1981; Mann et al. 1981; Danks 1983; Prohaska 1983a, 1983b, 1984). Copper therapy of Menkes' infants, up to now, has been ineffective. It is unclear whether maternal, fetal, and/or the interaction of maternal and fetal factors predispose the neonate to the decreased growth rate characteristics of the copper deficient state.

Laboratory mice have long been used as a mammalian model for growth (Eisen 1974, 1976) and selection (Eisen 1975; Falconer 1981) studies. An animal model of the human genetic disorder permits observations and study not possible with affected humans. There are at least five distinguishable alleles at the mottled locus in mice, any of which could be used to study the effects of a single gene upon copper metabolism, growth and development. These alleles are: (1) tortoise, Mo^{to}

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(Dickie 1954); (2) dappled, Mo^{dp} (Fraser et al. 1953; Phillips 1961); (3) brindled, Mo^{br} (Fraser et al. 1953; Falconer 1953); (4) viable brindled, Mo^{vbr} (Rowe et al. 1974) and (5) blotchy, Mo^{blo} (Russell 1960). A hierarchy of viability exists among the hemizygous males. Dappled (Mo^{dp}/Y) and tortoise (Mo^{to}/Y) mice die in utero, approximately 7 and 17 days, respectively prior to birth. Brindled (Mo^{br}/Y) and viable brindled (Mo^{vbr}/Y) mice survive the neonatal period but die at 12–14 days and approximately 100 days, respectively. Blotchy (Mo^{blo}/Y) mice survive for approximately 150 days (Rowe et al. 1974; Grahn et al. 1969). In tortoise mice, although the males die prenatally the heterozygous mutant females are generally viable and fertile and represent a heterogeneous group with varying degrees of expression of the mutant gene (Grahn et al. 1965).

The heterozygous tortoise females offer an opportunity to compare the effects of a single gene on litter size, birth weight, preweaning weight and fitness independent of differences in the maternal environment (Nash and Kidwell 1973; Goedbloed 1974, 1977; Prins and Van Den Hamer 1980). The results may allow a clearer understanding of MKHS and the copper requirement of the fetus, neonate, and adult.

Materials and methods

Experimental procedure

Mice progeny used in this study were from a single congenic strain C57BL/6J-Mo^{to} and were as genetically alike as possible, except for the known difference at the Mo locus. The progeny were derived from the mating of C57BL/6J-+/+ normal (N) females to C57BL/6J-+/Y normal males (N×N) and C57BL/6-Mo^{to}/+ mutant (M) females to C57BL/6J-+/Y normal males (M×N). Mating pairs were individually housed, fed a complete diet (Rockland mouse/rat diet, Winfield, IO), and allowed access to feed and water ad libitum. The male was removed when a vaginal plug was detected in the female, and the mated females were maintained separately until parturition and thereafter with offspring until weaning at 30 days postpartum.

Individual mice were sexed at birth (4 to 8 h postpartum) and classified by sex and genotype (Mo^{+}/Mo^{+}, Mo^{to}/Mo^{+}, Mo^{+}/Y), parity, and mating type, and were identified with a toe coding system. Each genotype was associated with an identifiable phenotype at birth. Mo^{+}/Mo^{+} (+/+ genotype) had straight vibrissae, female genitalia, and a solid coat color; the heterozygote Mo^{to}/Mo^{+} (To/+) had kinky vibrissae, female genitalia, and a mottled coat color; and Mo^{+}/Y had straight vibrissae, male genitalia, and a solid coat color. Due to the lack of dominance, homozygous (+/+) and heterozygous (To/+) females were phenotypically identifiable by their coat color (solid vs mottled coat). All genotypic identifications were further confirmed at weaning. Individual body weights (±0.05 g), litter size, and viability data were recorded at birth and on days 1 and 3, and at 3 day intervals thereafter to 30 days old. Artificial light was provided 14 h daily in a 25 °C temperature and 30% to 50% relative humidity controlled animal room.

Statistical analyses

In order to simplify the analyses and interpretation of the data, two separate sets of data were obtained for this study. The first set of data was selected primarily to determine if the tortoise gene, in the heterozygous females, would affect the prenatal and postnatal growth and development of their normal male and female progeny. Comparison 1 consisted of 76 litters of which 58 were from M×N and 18 from N×N parental matings (dam×sire). The litters were from parities 1 and 2. All offspring were phenotypically normal (+/+ female, +/Y male) but were from two different parental mating types (N×N and M×N). Mutant females produced from M×N mating were not included in this analysis.

Comparison 2 data were collected primarily to determine if female littermates differing only for the tortoise gene would manifest significant differences in body weight, growth rate, and development. This data set consisted of 85 litters from the M×N parental mating type only. These mice were either normal (+/+) or mutant (To/+) females and were born in 6 parities. Fifty-eight litters were common to both data sets, but normal male progeny (+/Y) were deleted from data set 2 to compare normal and mutant females.

Both data sets were analyzed by the general linear models (GLM) procedure of SAS (SAS Institute 1982). The model used for the analyses of data from set 1 (Comparison 1) was:

$$Y_{ijkl} = u + P_i + M_j + S_k + PM_{ij} + PS_{ik} + MS_{jk} + PMS_{ijk} + b_1 W_{ijkl} + b_2 L_{ijkl} + e_{ijkl}$$

where Y_{ijkl} = body weight measurement (g) at birth or at 3 day intervals; u = population mean; P_i = effect of the ith parity, i = 1, 2; M_j = effect of the jth mating type, j = 1, 2; S_k = effect of sex, k = 1, 2; PM_{ij}, PS_{ik}, MS_{jk}, PMS_{ijk} are two- and three-way interactions among parity, mating type, and sex, respectively; b_1, b_2 are multiple regression coefficients of Y_{ijkl} on W_{ijkl} (birth weight) and L (litter size), respectively; and e_{ijkl} = error term of the lth observation in subgroup ijk. Analysis of birth weight data did not include birth weight as a covariate in the model. Effects of sex, interactions with sex of mouse, and the covariates were removed from the above model prior to analysis of litter size and number of females and males in the litter. These litter traits were separately analyzed by a model including effects of mating type, parity, and mating type × parity interaction. Each litter was considered an experimental unit for this analysis. A chi-square test was also applied to determine if the frequency distribution of litter size or litter sex was independent of mating type or parity. The purpose of Comparison 1 was primarily to determine the significance of the maternal genotype on the growth of phenotypically normal mice produced from two different mating systems (N×N and M×N).

The model used for the analysis of data set 2 (Comparison 2) was:

$$Y_{ijk} = u + P_i + G_j + PG_{ij} + b_1 W_{ijk} + b_2 L_{ijk} + e_{ijk}$$

where Y_{ijk}, u, $b_1 W_{ijk}$, $b_2 L_{ijk}$, and e terms are as described earlier; P_i = effect of the ith parity, i = 1, . . ., 4; G_j = effect of jth genotype, j = 1, 2; and PG_{ij} = interaction between parity and genotype. Since a preliminary analysis of the data indicated no differences between parities 4, 5, and 6, the data from these parities were pooled in the final analysis. The purpose of Comparison 2 was primarily to determine the significance of the progeny genotype on the growth of phenotypically normal and mutant females produced from the M×N mating.

Results

Litter traits

The number of mice in a litter varied from 2 to 11 in a total of 103 litters used in the study (data not presented). Approximately 82% of the litters produced from M×N matings contained 5 to 8 sibling mice. In N×N matings, however, litter sizes were larger and 94% of the litters varied in number of mice from 6 to 11. A preliminary chi-square test indicated that litter size was influenced by the parental mating type.

The number of normal females in all litters pooled varied from 0 to 8. About 81% of the litters produced from the M×N mating had 1 to 3 normal females. In the N×N mating, 89% of the litters had 3 to 6 normal females. The chi-square test indicated that the number of normal females, mutant females, and normal males in the litter were all influenced by the mating type. The number of mutant females produced by the M×N matings varied from 0 to 5 and 84% of the litters consisted of 1 to 3 mutant females. the number of normal males in the litters varied from 1 to 6 in N×N and 0 to 4 in M×N matings. In the 85 M×N litters observed, 9 (11%) had no males while 85% of the total litters had 1 to 3 males. In the N×N mating type 94% of the litters had 2 to 6 males.

The effects of mating type and parity on litter characteristics are summarized in Table 1. Mating type influenced all litter traits significantly ($P < 0.01$). Size of the litter from N×N mating exceeded that of M×N mating by 30%. The statistical expectation for this observation was 25% since the offspring produced from the M×N mating were tortoise male (To/Y) which died prior to birth. The average number of normal females or males in the litter of N×N mating type was greater than that of M×N by more than two offspring. The small number of males in litters of the M×N mating is attributable to the lethal effect of the tortoise gene, but the smaller number of females was unexpected. The sex index (average difference between number of females and males in a litter) also differed between the two mating types. The index indicated an average of 2.4 more females in litters of N×N than in litters of the M×N mating type.

Overall, litter size increased by 20% from first to second parity (Table 1). The number of normal females per litter or the sex index did not change significantly over the two parities. The average number of males per litter, however, increased ($P < 0.01$) by 50% with increasing parity. Mating type×parity interaction was significant for sex index and number of males per litter. The changes in sex index was, however, in favor of number of males per litter in the N×N mating type (1.7 in parity 1 vs −0.8 in parity 2). The average number of males per litter did not change with the increase in parity in the M×N mating type (1.8 in parity 1 vs 5.2 in parity 2), but an increase of 73% (3.0 in parity 1 vs 1.9 in parity 2) was observed in the N×N mating type. No significant mating type×parity interaction was observed for litter size or the number of females per litter.

Comparison 1

Results of analyses of variance for preweaning body weights are presented in Table 2. Maternal genotype did not influence ($P > 0.05$) birth weight or body weight of the offspring up to 18 day old, but the effect was significant ($P < 0.01$) from 21 days to 30 days. Offspring produced from N×N matings were heavier ($P < 0.01$)

Table 1. Effect of mating type and parity on litter size and number of each sex per litter[a]

Effect	No. of litters	Litter size	No. of each sex/litter		Sex index[b]
			Female[d]	Male	
Mating typing[c]					
M×N	58	6.6±0.22	2.4±0.17	1.9±0.14	2.8±0.26
N×N	18	8.6±0.41	4.5±0.31	4.1±0.26	0.4±0.48
Difference		2.0**	2.1**	2.2**	−2.4**
Parity					
1	49	6.9±0.27	3.4±0.21	2.4±0.17	2.1±0.32
2	27	8.3±0.38	3.5±0.29	3.6±0.24	1.1±0.44
Difference		1.4**	0.1	1.2**	1.0

[a] Mean±SE
[b] Sum of To/+ and +/+ females minus +/Y males
[c] M and N refer to mutant and normal phenotypes. Mating types are indicated by dam×sire phenotypes
[d] Numbers indicate normal females only. Litter size − (No. of females + No. of males) = the average number of mutant females in the litter
** Difference between means significant at 0.01 probability level

Table 2. The least-squares analysis of body weight at various age intervals (Comparison 1)

Source	df	Birth weight	Body wt at various ages (days)											
			1	3	6	9	12	15	18	21	24	27	30
			F values and tests of significance											
Mating type (MT)	1	0.0	0.2	0.0	1.4	0.4	0.3	0.4	1.5	10.9**	15.7**	19.2**	19.5**
Parity (P)	1	83.5**	5.7**	39.1**	9.4**	7.4**	2.8**	4.8*	10.5**	8.2**	5.4*	6.4**	5.6*
MT×P	1	0.6	2.1	3.8	0.1	5.1*	6.8**	7.3**	8.9**	12.5**	12.2**	21.1**	20.3**
Sex	1	2.0	0.2	0.2	1.3	1.5	1.8	3.2	8.2**	20.9**	48.7**	98.0**	141.5**
MT×Sex	1	0.0	1.8	6.2**	4.9*	6.0**	3.6	6.8**	11.1**	11.9**	8.2**	8.9**	9.8**
P×Sex	1	0.9	0.7	0.6	0.4	0.5	0.1	0.0	0.0	0.1	0.3	0.8	0.3
MT×P×Sex	1	2.3	1.3	0.3	0.1	0.0	0.3	0.0	0.0	0.7	2.3	4.9*	2.4
Birth wt	1	–	1,231.8**	426.9**	184.0**	74.1**	42.6**	26.1**	15.6**	26.9**	32.0**	42.9**	49.0**
Litter size	1	28.8**	7.4**	24.5**	68.8**	60.8**	52.1**	45.1**	44.7**	32.7**	19.0**	13.3**	10.8**
Error[a]	491[b]	0.019	0.010	0.044	0.160	0.416	0.854	1.256	1.747	2.294	3.023	3.521	3.912
CV (%)		9.1	6.0	8.6	10.5	12.6	14.8	16.0	16.5	15.9	15.0	13.7	12.4
			Regression coefficients										
Birth wt (g)		–	1.19**	1.45**	1.81**	1.87**	2.04**	1.93**	1.77**	2.67**	3.34**	4.17**	4.70**
Litter size		−0.02**	−0.01**	−0.03**	−0.10**	−0.15**	−0.21**	−0.23**	−0.27**	−0.27**	−0.24**	−0.21**	−0.20**

[a] Values are mean squares

[b] Degrees of freedom ranged from 495 for birth weight to 463 for 30 day weight

*,** Defined as $P<0.05$ and $P<0.01$ for F values, and for the *t*-test of constants being significantly different from zero

than those from M×N mating during this period (Table 3). Parity significantly affected all preweaning weights and parity 2 offspring were heavier than parity 1 for all observed ages (Tables 2 and 3).

Mating type × parity interaction was not significant ($P>0.05$) prior to 9-days of age but was significant thereafter (Table 2). The increase in parity was associated with an increase in body weight of the offspring from N×N mating type. The response, however, was different for offspring from M×N mating type where no substantial change in body weight was associated with an increase in parity. Sex of mouse did not influence ($P>0.05$) body weight prior to 18 days old (Table 2). During 18 to 30 days however, males were heavier ($P<0.01$) than females (Table 3). The mean square for the interaction of mating type and sex of the offspring was significant for body weight at all ages except at birth, 1, and 12 days old (Table 2). This interaction provides evidence for differential sex responses at varying ages for the two mating types. Parity×sex and mating type×parity×sex interactions were not significant (except for 27-day weight) for all ages observed (Table 2).

Birth weight and litter size covariates were significant ($P<0.01$) for all ages used in the study (Table 2). The regression coefficients for birth weight were consistently positive and ranged from 1.19 at day 1 to 4.70 at day 30. All regression coefficients, however, were negative for litter size and ranged from −0.02 at birth to −0.27 at 18 or 21 days old. Relative variability for body weight measurements, as determined by coefficient of variation, was lowest (6.0%) at day 1 and highest (16.5%) at day 18 (Table 2).

Mortality rate of the offspring was not influenced by parental mating type or parity, but sex differences influenced mortality (Table 3). In this study, the observed mortality for females (7.2%) was higher than the value for males (4.1%).

Comparison 2

Results of the analyses of variance and least-squares estimates of means are shown in Tables 4 and 5, respectively. The mean square for mouse genotype was not significant ($P>0.05$) for birth weight, but was significant ($P<0.01$) for all other body weight measurements (Table 4). Normal females (+/+) were consistently heavier than mutant females (To/+) throughout the 30-day growth period (Table 5). Mortality was about 9 times greater for the tortoise (To/+) genotype than the normal (+/+) genotype (13.7 vs 1.5%).

The effect of parity was significant for all body weight measurements including birth weight (Table 4). Mice from parities 2 and greater were similar in body weight prior to 9 days of age (Table 5), but were sig-

Table 3. No of mice (n) and means ($\bar{X}$ in g) for birth weight (adjusted for litter size), body weights at various age intervals (adjusted for birth weight and litter size), and mortality rate (Comparison 1)

Trait	Mating type[a]				Parity				Sex			
	M×N		N×N		1		2		Female		Male	
	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$
Birth weight	358	1.52	146	1.52	309	1.45	195	1.59[c]	334	1.51	170	1.53
Body weight/ day old												
1	355	1.69	146	1.69	306	1.67	195	1.70[c]	332	1.69	169	1.69
3	354	2.44	145	2.45	304	2.37	195	2.53[c]	331	2.44	168	2.45
6	353	3.87	143	3.81	301	3.76	195	3.91[c]	329	3.81	167	3.86
9	353	5.20	137	5.15	300	5.07	190	5.29[c]	326	5.13	164	5.22
12	349	6.30	136	6.24	296	6.18	189	6.37[c]	322	6.20	163	6.34
15	348	7.11	136	7.03	295	6.92	189	7.22[c]	321	6.96	163	7.18
18	346	8.13	136	8.34	295	7.97	187	8.50[c]	319	8.03	163	8.44[d]
21	344	9.56	136	10.18[b]	295	9.60	185	10.14[c]	317	9.49	163	10.25[d]
24	340	11.62	136	12.48[b]	293	11.80	183	12.30[c]	313	11.38	163	12.72[d]
27	338	13.82	136	14.84[b]	292	14.04	182	14.63[c]	311	13.31	163	15.35[d]
30	337	16.11	136	17.19[b]	292	16.36	181	16.95[c]	310	15.36	163	17.95[d]
Mortality (%)		5.9		6.8		5.5		7.2		7.2		4.1

[a] As in Table 1
[b] Means of M×N and N×N mating types, within a row, differ ($P < 0.05$)
[c] Means of parity 1 and parity 2, within a row, differ ($P < 0.05$)
[d] Means of female and male mice, within a row, differ ($P < 0.05$)

nificantly heavier than parity 1 mice during this period. Mice from parities 1 and 2, however, did not differ significantly in body weight from 9 to 30 days. Mice from parities 3 and greater also did not differ significantly during this period. The latter groups, however, were significantly heavier than those from parities 1 and 2. Parity 3 mice had the lowest mortality (4.3%) and parity 4 and greater the highest (10.5%). The coefficient of variation ranged from 5.7 for 1 day to 14.4% for 24 day body weight.

The interaction mean square for genotype×parity was not significant for any body weight measurement (Table 4). Birth weight and litter size, as covariates, however, influenced all body weight measurements significantly ($P < 0.01$). The regression coefficients for birth weights were all positive as in Comparison 1 and ranged from 1.15 for day 1 weight to 5.05 for day 30. The regression coefficients for litter size were consistently negative as they were in Comparison 1 and ranged from –0.03 for birth weight to –0.43 for 18 day body weight (Table 4).

Discussion

Growth, development, and survival in humans and mice are disrupted by several mutations with pleiotropic effects that alter copper metabolism (Mann et al. 1979; Rauch 1983; Prohaska 1986). In this study, the detectable differences in progeny weight (growth) and adult female reproductive performance were attributable to the effect(s) of a single gene segregating. The tortoise gene, present in the heterozygous females did not significantly affect birth weight of normal male and female progeny.

In Comparison 1 (normal offspring only), birth weight and body weights were similar for both mating types up to 18 days old. Thereafter, body weights were lower for offspring from tortoise dams. This may be attributed to a partial self-initiated weaning of mice prior to 30 days old. This hypothesis was supported by the change in coefficient of variation which decreased after day 18 and also litter size regression which increased through day 18 and decreased thereafter. In Comparison 2 homozygous normal and heterozygous mutant females sharing the same uterine environment of a heterozygous mutant dam did not differ significantly in birth weight. The effect of the sibling genotype on all other body weight measurements, however, was significant. This observation supports the hypothesis that the mottled locus, particularly the tortoise gene, has no detectable affect on birth weight.

The tortoise gene, however (Comparison 2), significantly reduced the growth rate at which the offspring developed postpartum. Since birth weights at parturition were similar for normal and mutant females, growth retardation of the tortoise mice may have been due to the copper deficiency in postpartum developing offspring (Danks 1977; Mann et al. 1981; Prins and Van Den Hamer 1981; Danial et al. 1982; Prohaska 1983a, b, 1984; Rauch 1983; Prohaska 1986).

Table 4. The least-squares analysis of the body weights of the female mice from M×N mating type at various age intervals (Comparison 2)

Source	df	Birth weight	Body wt at various ages (days)										
			1	3	6	9	12	15	18	21	24	27	30
			F values and tests of significance										
Genotype (G)	1	0.2	11.4**	53.7**	107.4**	143.3**	139.6**	151.2**	239.0**	225.2**	159.1**	112.6**	94.7**
Parity (P)	3	45.1**	4.7**	12.2**	7.8**	10.5**	10.7**	12.0**	9.1**	4.0**	2.5*	2.5*	2.7*
G×P	3	1.8	0.9	0.7	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.2
Birth wt	1	–	832.1**	236.7**	190.2**	98.8**	71.4**	56.6**	31.3**	41.9**	36.2**	33.5**	41.6**
Litter size	1	34.9**	19.4**	27.8**	101.8**	133.8**	140.4**	136.4**	120.6**	57.7**	24.7**	28.0**	18.4**
Error[a]	389[b]	0.017	0.010	0.056	0.148	0.324	0.592	0.849	1.196	1.708	2.532	3.143	3.55
CV (%)		8.4	5.7	9.3	9.7	10.7	11.9	12.7	13.6	14.1	14.4	13.8	12.6
			Regression coefficients										
Birth wt		–	1.15**	1.45**	2.12**	2.26**	2.61**	2.79**	2.47**	3.43**	3.95**	4.26**	5.05**
Litter size		−0.03**	−0.02**	−0.04**	−0.14**	−0.23**	−0.32**	−0.38**	−0.43**	−0.35**	−0.29**	−0.34**	−0.29**

[a] Values are mean squares
[b] Degrees of freedom ranged from 390 for birth weight to 358 for 30-day weight
*,** $P<0.05$, and $P<0.01$, respectively for F values and for the t-test of constants being significantly different from zero

Table 5. No of mice (n) and least squares means ($\bar{X}$ in g) for birth weight (adjusted for litter size), and for body weights at various age intervals (adjusted for birth weight and litter size), and mortality rate (Comparison 2)

Trait	Genotye				Parity							
	To/+		+/+		1		2		3		≧4	
	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$	n	$\bar{X}$
Birth wt	205	1.57	194	1.56	154	1.45[c]	100	1.59[b]	69	1.61[b]	76	1.62[b]
Body wt/days old												
1	204	1.73	193	1.77[a]	152	1.72[c]	100	1.76[b]	69	1.77[b]	76	1.75[b]
3	203	2.46	193	2.64[a]	151	2.42[c]	100	2.57[b]	69	2.61[b]	76	2.60[b]
6	199	3.78	193	4.20[a]	150	3.82[c]	100	4.01[b]	67	4.06[b]	75	4.08[b]
9	199	5.02	193	5.75[a]	150	5.15	100	5.27[c]	67	5.53[b]	75	5.58[b]
12	193	6.05	192	7.02[a]	146	6.29	100	6.30	66	6.71	73	6.84
15	192	6.71	192	7.92[a]	145	7.01[c]	100	7.00[c]	66	7.59[b]	73	7.66[b]
18	190	7.24	192	9.06[a]	145	7.77[c]	98	7.89[c]	66	8.48[b]	73	8.46[b]
21	187	8.27	191	10.39[a]	145	9.08[c]	96	9.07[c]	66	9.58[b]	71	9.60[b]
24	181	10.00	191	12.19[a]	143	10.88[c]	94	10.84[c]	66	11.26[c]	69	11.41[c]
27	178	11.85	191	13.92[a]	142	12.70[c]	93	12.67[c]	66	12.79[b,c]	68	13.39[b,c]
30	177	13.94	191	15.95[a]	142	14.78[c]	92	14.60[c]	66	14.97[b]	68	15.44[b]
Mortality (%)		13.7		1.5		7.8		8.0		4.3		10.5

[a] Genotype means, within a row, differ ($P<0.05$)
[b,c] Parity means, within a row, differ ($P<0.05$)

The significant parity effects on litter size, birth weight, and body weight at all ages, detected in both comparisons in this study, are consistent with other observations (Bandy and Eisen 1984a, b; Goedbloed 1974). Mortality rate was not influenced by genotype of the dam or parity; however, sex differences were observed. Female mortality was greater than male mortality, and tortoise mortality was about 9-fold greater than normal female mortality during pre-weaning development. The relatively high mortality rate of the heterozygous tortoise females (To/+) in the mouse supports the observed invariably fatal course during infancy or early childhood in male humans with MKHS (Danks et al. 1972; Anonymous 1981).

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