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Parental age and recombination frequency in the house mouse

By MARGARET E. WALLACE, FELICITY J. MacSWINEY
Department of Genetics, University of Cambridge
AND R. G. EDWARDS
Department of Physiology, University of Cambridge

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SUMMARY

The relationship between parental age and recombination frequency in the offspring of mice has been studied using backcrosses to heterozygous males or females. The mice were allowed to breed until they became infertile. Data for several chromosomes were analysed, mostly from a stock carrying five markers covering approximately three-quarters of the length of chromosome 2.

Analyses of two-point recombination ratios or of multi-point interference ratios revealed no consistent age-related heterogeneity in offspring of male or female heterozygotes. A significant age-related heterogeneity was detected in the offspring of female heterozygotes but not of males, when the number of offspring with no detectable recombination was compared to those with one or more. This difference between the sexes could be related to earlier cytological observations on chiasma frequency in oocytes and spermatocytes. The significance of these findings for the analysis of follicular growth in mammals and in the origin of human trisomic conditions is discussed.

1. INTRODUCTION

Differences have been reported between male and female in mice in the frequency of recombination between various loci, although some disagreement exists in the literature (Robinson, 1972). One difference between the sexes could arise through an age-related change in recombinational events in females without a corresponding change in males, a situation indicated in some published reports. We wish to present data on changing recombinational events with maternal and paternal age, analysed in several ways.

Changes in recombination and interference frequency were studied in eighteen segments among eight chromosomes. In chromosome 2, marked with five mutants, multiple-recombination changes with age were studied in two new ways.

2. MATERIAL AND METHODS

Linkage stocks used for the analysis

Linkage backcross data were collected from the long term records at the Department of Genetics, Cambridge, the Institute of Animal Genetics, Edinburgh, and the M.R.C. Radiobiological Research Unit, Harwell. Data were selected in which heterozygous mice had been allowed to breed until infertile, as shown in Tables 4 and 5.

Table 1. *Linkage relations between markers*

Chromosome no.	Markers and recombination values (%)												Source of data
2	C	Close	*Sd*	20	*fi*	15	*ro*	3	*we*	11	a^t	22	*Ra*	Cambridge
4	C	40+	*b*	8	*Ps*	2	*m*							Cambridge
6	C	4	*Sig*	31	*Lc*	11	Mi^{wh}							Harwell
7	C	22++	*p*	14	c^{ch}	3	*sh*-1	16	*fr*					Cambridge
8	C	32	*Os*	28	E^{so}									Harwell
9	C	2	*cw*	37	*se*	5	*tk*							Edinburgh
11	C	4	*wa*-2	27	*vt*	3	*sh*-2							Cambridge
15	C	55	*bt*	8	*Ca*									Cambridge

C = centromere. Chromosome no. 2: *Sd* = Danforth's short tail, *fi* = fidget, *ro* = rough, *we* = wellhaarig, a^t = tan-belly, *Ra* = ragged. Chromosome no. 4: *b* = brown, *Ps* = polysyndactyly, *m* = misty. Chromosome no. 6: *Sig* = sightless, *Lc* = lurcher, Mi^{wh} = white. Chromosome no. 7: *p* = pinkeyed dilution, c^{ch} = chinchilla, *sh*-1 = shaker-1, *fr* = frizzy. Chromosome no. 8: *Os* = oligosyndactyly, E^{so} = sombre. Chromosome no. 9: *cw* = curly whiskers, *se* = short ear, *tk* = tail-kinks. Chromosome no. 11: *wa*-2 = waved-2, *vt* = vestigial tail, *sh*-2 = shaker-2. Chromosome no. 15: *bt* = belted, *Ca* = caracul.

All the data concern laboratory stocks entirely, except in cases where a wild-type chromosome came into the heterozygote from the natural wild stock: in Tables 2 and 3, SF stands for the inbred wild strain San Franciscan, P for the random bred wild strain Peru-Atteck, and PBI for the random bred wild strain Plant Breeding Institute. The origins of these strains are given in Wallace (1971) and Wallace & MacSwiney (1976).

The gene markers used are shown in Table 1, and the sources of data. The distance between markers and between the end marker and centromere are derived by adding recombination values between adjacent segments. The larger values given between centromere and marker are probably over-estimates compared with those which would be obtained if closer markers were available. The shorter values may be under-estimates since they are largely obtained from translocation data where crossing over may be suppressed, but they provide a rough guide to the relative lengths of segments and the relation of each segment to the centromere. These values are based on information given in Cattanach & Moseley (1973), Cattanach & Moseley (1974*a*,*b*,*c*), Green (1975), Lyon, Butler & Kemp (1968), Lyon & Hawkes (1970), Robinson (1972, pp. 206, 239), Searle & Beechey (1971) and Searle, Ford & Beechey (1971).

Recombination and interference

Progeny data were grouped according to the following ages of their heterozygous parents: up to 3 months, 3–4 months, 4–6 months, 6–8 months, 8–10 months, 10–12 months and over 12 months. Where data were sparse for the later months, they were pooled as shown in Tables 4 and 5.

The data were then analysed according to the method described by Wallace (1957). Adjacent markers are designated *A*, *B*, *C* etc., and segments numbered sequentially, e.g. *A*-1-*B*-2-*C* etc. A recombinational event in a segment is then identified as (1) i.e. occurring in segment 1 only, (2) in segment 2 only, etc. Recombinations occurring simultaneously in two or more segments can be identified, e.g. (1,2) in segments 1 and 2, and thus the total number and position of recombinations can be determined for each offspring. With five marker genes, the number of possibilities is thus: one with no recombinations (i.e. none detected between any of the markers), four different single recombinations, six different doubles, four different trebles and one quadruple.

Three different phenomena were measured. First, effects on the viability of young carrying the marker genes were determined by adding the phenotypes for each marker gene; for example, the ratio $A:a$ is obtained by adding all those progeny with phenotypes *A* and all those with phenotypes *a* regardless of their phenotypes in respect of B,b,C,c, etc. Each single-factor ratio was compared with the 1:1 expectation for full viability and penetrance.

Secondly, the recombination value for each adjacent segment was obtained by adding the pairs of phenotypes complementary for all the relevant marker genes; the ratio of non-recombinant phenotypes to recombinant ones was found for each segment, irrespective of events in neighbouring segments.

Thirdly, the interference ratio for each pair of segments was obtained. For five markers, there are six double recombinations, and each was considered separately. Simultaneous recombinations in segments 1 and 2 were compared with all other events; next, recombinations in 1 and 3 were compared similarly, etc., thus resulting in six interference ratios. The triples were studied similarly, e.g. simultaneous recombinations in segments 1, 2 and 3 being compared with the sum of all other events.

Each ratio, of each of the three kinds, was studied for heterogeneity by using a $2 \times j\chi^2$, where j is the number of age intervals. Observations in a few cases were too small for a valid χ^2 to be done; in all, 132 heterogeneity χ^2 were done in females and 175 in males.

The single-factor ratios for marker genes must be analysed first. The recombination and interference values in the segments bounded by the markers are distorted if more than one single factor ratio is disturbed by relative inviability, or one or more by impenetrance of the relevant mutant genes (see the section on design in Wallace, 1957). Any disturbance of these ratios by age can thus distort the true changes of recombination and interference by age. The accuracy of these two types of change proven by heterogeneity χ^2 must therefore be judged against the

results of the heterogeneity analysis for the viability and penetrance of the marker genes.

Since published cases of change with age give no reason to assume a consistent linear trend, and in fact a curvilinear trend is suggested to explain certain inconsistencies (Wallace 1957, p. 240), the intention was to detect merely heterogeneity in relation to age.

Total number of recombinations in chromosome 2 with increasing age

Data on the five markers in chromosome 2 can be examined in another way. The region *Sd-Ra* is about 90 cM long (Wallace, 1958) which is near the likely full length of this chromosome, the average based on chiasmata per chromosome being 119 for females and 99 for males (Robinson 1972, pp. 297, 299). All recombinational events thus reflect closely all chiasmata in this chromosome. These data thus lend themselves to an estimate of the number of recombinations per offspring occurring in different age groups.

In most offspring, one or more recombinations were detected, and the number of recombinations in all offspring could be simply calculated. Offspring having 1 recombination were credited with one, those with a double recombination were credited with 2, etc.

The total number of recombinations (T), divided by the number of progeny in which they occurred (N), gave the average number of recombinations per individual; this value was studied in relation to maternal age and paternal age as shown in Tables 4 and 5. $2 \times j$ heterogeneity tests were done in which the two classes are T (or T* see Tables 4 and 5) and N, and j the number of age intervals. A test for regression of T/N on age was also done in females.

In some offspring no recombinations were detected, but it is unlikely that none actually occurred; presumably at least one chiasma arose in chromosome 2 in all progeny. Failure to detect at least one recombination in some offspring must have been due to its terminal location, i.e. outside the length of chromosome covered by the marker genes, or because of double recombination between two adjacent markers. The ratio of offspring showing no recombination to those with one or more was therefore studied separately in Tables 6 and 7. Each ratio was studied for heterogeneity by using the $2 \times j\chi^2$ where j is the number of age intervals. A χ^2 test for linearity (devised by R. A. Fisher: formula given on p. 236 of Wallace 1957) was also applied to the data in Table 6.

3. RESULTS

Most $2 \times j$ heterogeneity tests for marker viability and for recombination and interference ratios (Tables 2 and 3), gave an insignificant result, indicating no age-related disturbance. The few significant results are shown. Thus, the entry *fi**** in Table 3, column 3(*a*) indicates that the ratio of fidget to normal offspring, i.e. *fi*: + is disturbed in relation to age, the heterogeneity χ^2 being significant with a probability $< 0{\cdot}01$. The adjacent entry 'none' under 'Trend' in the same column

means that there appeared to be no overall upward or downward trend with age in this ratio as judged by eye. Similarly, the entry *fi-we** in the adjacent column 3(*b*) of Table 3 shows that the ratio of non-recombinants:recombinants for the segment *fi-we* appears to change with age, the heterogeneity χ^2 giving a probability of $< 0{\cdot}05$, although the adjacent entry 'None' means that there was no overall upward or downward trend with age as judged by eye. Similarly, the entry 2

Table 2. *Data for female heterozygotes.*

1.		2.	3. Significant heterogeneity tests					
			(*a*)		(*b*)		(*c*)	
Chromosome number	Markers and linkage phase (*)	No. bred	Viability	Trend	Recomb'n	Trend	Interf'ce	Trend
2	*Sd/fi we a^t Ra*	100	—	—	*Sd-fi**	None	2 and 4*	None
	Sd a^t Ra/fi we	271	*Ra**	None	—	—	2 and 4**	None
	Combined†	732			—	—	—	—
	Sd/fi Ra	269	*Sd***	Down	—	—	—	—
	Sd fi/Ra	92	—	—	—	—	—	—
	Sd Ra/fi	590	*fi*, Ra**	None	*fi-Ra**	None	—	—
	Sd fi/Ra	155	—	—	—	—	—	—
	Combined	1106			—	—	—	—
	Sd fi we a/SF	846	—	—	*Sd-fi***	Down	—	—
	Sd fi we a/P	705	—	—	—	—	—	—
	fi ro/SF	741	—	—	—	—		
	fi ro/P	1046	—	—	—	—		
4	*Ps/b m*	729	—	—	—	—	—	—
	b m/SF	637	—	—	*b-m***	Down		
	b m/P	572	—	—	*b-m****	Down		
7	*p c^{ch} sh-1 fr*/PBI	2595	—	—	—	—	—	—
	p c^e/SF	741	—	—	—	—		
	p c^e/P	1046	—	—	—	—		
9	*cw se tk*/+	1157	—	—	—	—	—	—
11	*wa-2 vt sh-2*/+	1490	—	—	—	—	—	—
15	*bt Ca*/SF	215	—	—	—	—		
	bt Ca/P	266	—	—	—	—		

* $P < 0{\cdot}05$, ** $P < 0{\cdot}02$, *** $P < 0{\cdot}01$.

† includes phases (not shown) with small numbers of progeny.

(*) Initials SF, P, PBI and + refer to Wild-type chromosomes as described in Methods.

and 4* in column 3(*c*) means that the ratio between the number of simultaneous recombinations in segments 2 and 4 and the number of all other events change with age, the heterogeneity χ^2 having a probability of $< 0{\cdot}05$, although the adjacent entry 'None' indicates no overall upward or downward trend with age.

Data were omitted where the number of progeny for a particular phase was too small for validity in most of the statistical tests, and nearly all bodies of data thus concern more than 100 progeny. The smaller numbers of progeny are included in the 'Combined' totals in the tables, in addition to the discrete totals shown; the

members of complementary phenotypes are pooled, together with the small numbers, in order to produce larger classes for relevant tests.

Data in these tables make no case in the genome as a whole for a consistent upward or downward trend in recombination or interference with age. The number

Table 3 *Data for male heterozygotes*

1.		2.	3. Significant heterogeneity tests					
			(a)		(b)		(c)	
Chromosome number	Marker and linkage phase (*)	No. bred	Viability	Trend	Recomb'n	Trend	Interf'ce	Trend
2	*Sd/fi we a^t Ra*	124	—	—	—	—	2 and 4***	None
	Sd a^t/fi we Ra	151	—	—	*Sd-fi***	None	—	—
					*fi-we**	None		
	Sd fi we/a^t Ra	318	—	—	—	—	—	—
	Sd fi a^t/we Ra	158	a^t**	None	—	—	—	—
	Sd we a^t/fi Ra	274	*fi****	None	*fi-we**	None	—	—
	Sd a^t Ra/fi we	324	*Sd**	None	—	—	—	—
	Sd we a^t Ra/fi	178	—	—	—	—	2 and 4*	None
	Sd fi we a^t Ra/+	150	*Sd***	None	—	—	—	—
	Combined†	1900			—	—	—	—
	Sd/fi Ra	463	—	—	—	—	—	—
	Sd fi/Ra	146	—	—	—	—	—	—
	Sd Ra/fi	602	*Ra**	None	*Sd-fi****	None	—	—
					*fi-Ra**	None		
	Sd fi Ra/+	149	—	—	—	—	—	—
	Combined	1360			—	—	—	—
	fi ro/SF	649	—	—	—	—		
	fi ro/P	452	—	—	—	—		
4	*b m*/SF	1298	—	—	*b-m****	Down		
	b m/P	1940	—	—	—	—		
6	*Sig Lc* Mi^{wh}/+	1034	—	—	—	—	—	—
7	*p c^{ch} sh-1 fr*/PBI	424	*fr**	None	—	—	—	—
	p c^e/SF	649	—	—	—	—		
	p c^e/P	452	—	—	—	—		
8	*Os* E^{so}/+	3284	—	—	—	—		
15	*bt Ca*/SF	1148	—	—	—	—		
	bt Ca/P	1539	—	—	—	—		

* $P < 0{\cdot}05$, ** $P < 0{\cdot}02$, *** $P < 0{\cdot}01$.

† includes phases (not shown) with small numbers of progeny.

(*) Initials SF, P, PBI and + refer to Wild-type chromosomes as described in Methods.

of significant χ^2 values, at the three levels, obtained (total: 11 for females and 14 for males) was close to the number expected by chance (total: 10·5 for females and 14·1 for males). There is also no case for trend in a particular chromosome segment, because of its low probabilities for χ^2, despite the apparently consistent downward trend for the segment *b-Ps-m* (chromosome 4).

Total number of recombinations with increasing maternal and paternal age

The numbers of recombinations in chromosome 2 in the offspring of male and female heterozygotes are shown in Tables 4 and 5. Most offspring had none, one or two recombinations; three or four were rarely detected. The average number of recombinations per offspring is shown for each age in the penultimate column of

Table 4. *Offspring of heterozygous female mice: numbers of recombinations detected in chromsome 2*

Maternal age (months)	Number of recombinations in offspring 0	1	2	3	4	Total no. of recombinations (T)	Total no. of offspring (N)	T/N	T*/N
Up to 3	50	72	27	1	0	129	150	0·86	1·53
3–4	35	73	21	1	0	118	130	0·91	1·45
4–6	104	107	41	3	0	198	255	0·78	1·59
6–8	37	73	16	3	0	114	129	0·88	1·46
8–10	20	18	10	0	0	38	48	0·79	1·63
10 and over	8	7	3	0	0	13	18	0·72	1·61
Total	254	350	118	8	0	610	730		

T*: Crediting two recombinations to those offspring with none.

Table 5. *Offspring of heterozygous male mice: numbers of recombinations detected in chromosome 2*

Paternal age (months)	Number of recombinations in offspring 0	1	2	3	4	Total no. of recombinations (T)	Total no. of offspring (N)	T/N	T*/N
Up to 3	62	93	23	2	1	149	181	0·82	1·52
3–4	97	115	42	1	0	202	255	0·79	1·55
4–6	172	233	75	3	0	392	483	0·81	1·53
6–8	153	248	63	0	0	374	464	0·81	1·47
8–10	108	152	39	0	0	230	299	0·83	1·49
10 and over	80	97	34	5	0	180	216	0·83	1·57
Total	672	938	276	11	1	1527	1898		

T*: Crediting two recombinations to those offspring with none.

the tables. There was no significant heterogeneity, in either sex for the average number of recombinations per offspring. (χ^2 for 4 d.f. for females = 1·306, $P > 0·8$; χ^2 for 5 d.f. for males = 0·439, $P > 0·99$). The average number of recombinations per offspring, when those with none were assumed to have had two, is shown for each age in the last column. Again there was no significant heterogeneity for either sex. (χ^2 for 4 d.f. for females is 0·960, $P > 0·9$; χ^2 for 5 d.f. for males is 0·679, $P > 0·98$).

The regression test for T/N on age in females, where the heterogeneity χ^2 is large, gives a downward trend, which, however, is not quite significant ($P > 0{\cdot}1$). In males, where the heterogeneity χ^2 is small, there is no regression trend.

Ratio of offspring with no recombinations to those carrying one or more

Significant heterogeneity was detected when the number of offspring without recombinations was compared with those carrying one or more at various maternal ages (Table 6, $P < 0{\cdot}05$). The ratio appeared to increase with maternal age, but the χ^2 test for an upward linear trend was insignificant ($P > 0{\cdot}3$). The nature of the change with age does not appear to be simple. No heterogeneity was detected in the offspring of heterozygous males of increasing age (Table 7, $P > 0{\cdot}05$).

Table 6. *Offspring of heterozygous female mice: ratio of those with no recombinations to those with one or more*

Age (months)	Number with no recomb-inations	Number with one or more recombinations	Ratio	Probability of homogeneity
Up to 3	50	100	0·50	
3–4	35	95	0·37	
4–6	104	151	0·69	
6–8	37	92	0·40	< 0·05
8–10	20	28	0·71	
10 and over	8	10	0·80	

Table 7. *Offspring of heterozygous male mice: ratio of those with no recombinations to those with one or more*

Age (months)	Number with no recomb-inations	Number with one or more recombinations	Ratio	Probability of homogeneity
Up to 3	62	121	0·51	
3–4	97	158	0·61	
4–6	172	311	0·55	
6–8	153	311	0·49	⩾ 0·05
8–10	108	191	0·57	
10–12	44	78	0·56	
12 and over	36	58	0·62	

4. DISCUSSION

Our data cover 18 segments over 8 chromosomes, and reveal no consistent age-related trend in either sex when two-point recombination and multi-point interference ratios are studied.

Published data are no more consistent. Reid & Parsons (1963) were the only authors studying a chromosome not represented in our work, namely chromosome 1, marked by leaden, *ln*, and fuzzy, *fz*. They found a significant difference in recombination between the sexes with age, but the decrease with maternal age

and increase with paternal age were not significant when considered separately. Other published data from chromosome 2 utilize segments overlapping with those studied here, but conclusions are inconsistent with ours. Fisher (1949) found a decrease in recombination from about 11 % to 2 % in both sexes for the segment bounded by agouti and undulated, *un*. Bodmer (1961) studied maternal age only and found a decrease for the segment bounded by fidget and pallid, *pa*, from 32 %–22 %. Wallace (1957) found an increase in males in recombination for the fidget-agouti segment but no change in females, and suggested that curvilinear trends might be worth considering. We conclude that age-related changes vary according to strain, or that all the significant changes in the published and present work, taken in conjunction with the far greater number of insignificant changes, are entirely accountable by chance.

Perhaps age-related changes are too subtle to be discerned by studies of recombination and interference involving markers spanning only a small part of the chromosome. Events concerning markers spanning the whole, or a large part of the chromosome, may have to be studied. Our analysis, comparing the number of offspring with no recorded recombinations with the number having one or more (chromosome 2: $\frac{3}{4}$ of its length marked, Tables 6 and 7), showed a significant age-related heterogeneity in offspring of females but not of males. Fluctuations thus occur in the number of recombinations in oocytes of female mice but not in spermatocytes of males. Progeny at some ages of females, may therefore tend to possess a single recombinant lying distal to the area covered by the marker genes. Alternatively, the lack of detectable recombinations might arise through double crossovers between adjacent markers.

Our observations on the recombination frequency and parental age are relevant to those made earlier on chiasma frequency and parental age in mice (Henderson & Edwards, 1968; Luthardt & Donahue, 1973). The number of chiasmata declined, chiasma position was more terminal, and univalents were found in oocytes of aging females. Similar effects were not observed in males. Chiasmata might undergo terminalization during the long dictyotene stage in the adult female, and so explain these changes in number and position of chiasmata with increasing maternal age. There appears to be little direct evidence of terminalization in many species, and a close relationship evidently exists between the numbers of chiasmata and recombinations (e.g. Henderson, 1970).

The decline in chiasma frequency with maternal age has implications for the manner whereby follicles and oocytes are utilized in the mammalian ovary. It implies that a regularity exists in the growth of ovarian follicles throughout reproductive life, those containing oocytes with few chiasmata being concerned with senescence. The data on chiasma frequencies must be confirmed by studies on recombination frequencies to ensure that terminalization of chiasmata does not occur. Our present study reveals heterogeneity in recombination frequency in relation to maternal age, but we cannot detect a linear decline. A problem arises in the studies on recombination frequencies, because females become infertile at about 12 months and males soon afterwards. Data are needed on very old parents,

and studies are now in progress extending the reproductive span by transferring embryos from sterile aged females into young recipients.

A clinical consequence of the conservation of oocytes with few chiasmata towards the end of the reproductive life of the female concerns the origin of many forms of human trisomy with increasing maternal age (Boué, Boué & Lazar, 1975). Chromosomal non-disjunction at anaphase of the first meiotic division would be more likely to occur in oocytes with few chiasmata, i.e. in those of older females, and the association between trisomy and maternal age would thereby be explained.

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