Genet. Res., Camb. (1961), **2**, *pp.* 122–126
Printed in Great Britain

Tipsy, a new mutant in linkage group VII of the mouse

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(*Received* 12 *September* 1960)

The large collection of inherited locomotory disorders now known in the mouse can be placed roughly into three main categories: (i) the waltzer-shaker mutants, of which at least thirteen independent members are now known (Grüneberg, 1956), (ii) a group including dilute lethal, jimpy, jittery and Trembler, in which the syndrome typically includes convulsions, and (iii) mutants which walk unsteadily, often with a tremor or swaying movements, which may or may not be succeeded by ataxia, but without convulsions. Eight conditions of this type have already been described and the tipsy mutant is clearly another member of this last group. The present paper describes its abnormal behaviour and discusses its linkage relationships. Preliminary data on the inheritance and linkage relations of tipsy have been reported by Carter (1957, 1958) in private communications.

ORIGIN AND DESCRIPTION

Tipsy mice first appeared in 1956 among the F_2 offspring of a male carrying simultaneous mutations at the dilute and short-ear loci, which was one of the control offspring in a 37·5 r chronic gamma irradiation specific locus experiment. This male had been outcrossed to females A and B, F_1 offspring from a strain C3H/H × 101/H mating. Out of eight F_1 matings from A's progeny, two segregated for tipsy. With B, however, none out of five F_1 matings segregated, neither did any of six matings between A progeny and B progeny. Thus the mutant gene was probably derived from female A.

Tipsy mice can be distinguished from normals with some certainty at 6–8 days of age, when youngsters start active crawling. Instead of moving the hind-limbs alternately, the mutant flexes and extends both limbs together, producing what is best described as a 'rabbit gait'. About 4 days later a second characteristic defect appears, namely a tendency for the front part of the body to sway from side to side. There is marked variation with respect to this character. In severely affected animals there is an almost continuous rhythmic swaying, which leads to a reeling gait. The mutant takes an S-shaped course, first staggering over in one direction and then in the other, and occasionally falling over on its side. In other tipsy mice there is just an occasional side-to-side sway, with no obvious precipitating factor. The tendency to sway grows less in older adult mutants, disappearing completely in some. The rabbit-like gait, however, continues throughout life but is often interspersed at all ages with more or less normal locomotion. Mallyon (1953) reported

finding mice with rabbit gait in a stock carrying Fused (*Fu*), but it is clear from his description that a different entity is involved.

Tipsy mice can swim normally and are not deaf. When young ones are turned over on their back, however, they take decidedly longer than normals to right themselves. Moreover, when put down after being held up by the tail and gyrated, tipsy mice show an exaggerated sway in the direction of rotation and back again. The postural reaction when suspended by the tail (as described by Lyon, 1951) seems normal in tipsies; but their landing reaction, when held by the tail and quickly lowered towards a solid surface, is sometimes poorly developed.

SEGREGATION AND LINKAGE

The tipsy character is due to a fully recessive gene with 100% penetrance. Homozygotes of both sexes are fertile and when crossed have produced 86 tipsy and no normal offspring. Back-crosses of heterozygotes gave 49 tipsy and 52 normal, in good agreement with expectation. The symbol *ti* has been given to the gene concerned.

Crosses were made to the following mutant stocks for linkage tests: (i) dilute, short-ear (*d se*), (ii) White, Caracul, Brachyury (Mi^{wh} *Ca T*), (iii) Viable dominant spotting, Ragged, Rex (W^{v} *Ra Re*), with or without Danforth's short-tail (*Sd*). The results (Table 1) show that tipsy is fairly closely linked to Rex. Rex-tipsy recombination frequencies in the two sexes do not differ significantly and figures can therefore be combined, giving an overall frequency of $20{\cdot}23 \pm 1{\cdot}52\%$. Using Kosambi's (1944) transformation, this corresponds to a *Re–ti* map-distance of 21·45.

A three-point linkage test was then carried out to determine the position of *ti* with respect to other linkage group VII loci, namely vestigial (*vt*) and waved-2 (*wa-2*). When $\frac{+\ +\ +}{ti\ vt\ wa\text{-}2}$ females were crossed to males homozygous for all three recessive genes, offspring of the following phenotypes were obtained:

+	*ti*	*vt*	*wa-2*	*ti vt*	*ti wa-2*	*vt wa-2*	*ti vt wa-2*	total
258	26	4	63	66	1	23	164	605

ti shows $8{\cdot}93 \pm 1{\cdot}16\%$ recombination with *vt* and $29{\cdot}42 \pm 1{\cdot}85\%$ with *wa-2*, while *vt* and *wa-2* show $22{\cdot}15 \pm 1{\cdot}69\%$ recombination. So the order of loci must be *ti..vt..wa-2*. Further, since *Re* shows 21·7% recombination with *vt* (Michie, 1952) and *ti* shows only 9%, *ti* must lie between *Re* and *vt*.

DISCUSSION

Table 2 summarizes data on linkage relationships in group VII. In addition, Wright (1947) reported recombination frequencies in excess of 50% between *sh-2*, *wa-2* and sex. The results given in Table 2 are in fairly good agreement with each other, apart from those of Dickie (1955) on Alopecia (*Al*). Dickie found that Alopecia behaved in a very anomalous manner in linkage experiments, showing apparent linkage with members of several linkage groups; she discusses possible reasons for

Table 1. *Tests for linkage between tipsy* (ti) *and other mutants* (m)

Linkage group	Heterozygous parent	Phenotypes of progeny: $m+$	$+ti$	$++$	$m\,ti$	Total	Recombination frequency (%)
II	$\frac{d\ +}{+\ ti}$ ♂	46	39	43	48	176	53·2 ± 3·1
	$\frac{+\ +}{d\ ti}$ ♂	18	32	19	20	89	
	$\frac{d\ +}{+\ ti}$ ♀	31	33	36	33	133	51·9 ± 4·3
III	$\frac{W^v\ +}{+\ ti}$ ♂	42	61	40	35	178	42·1 ± 3·7
	$\frac{W^v\ +}{+\ ti}$ ♀	6	8	8	6	28	50·0 ± 9·4
V	$\frac{Ra\ +}{+\ ti}$ ♂	41	37	35	44	157	50·3 ± 4·0
	$\frac{Ra\ +}{+\ ti}$ ♀	15	12	14	11	52	48·1 ± 6·9
	$\frac{Sd\ +}{+\ ti}$ ♂	15	25	10	17	67	40·3 ± 6·0
	$\frac{Sd\ +}{+\ ti}$ ♀	6	8	11	5	30	53·3 ± 9·1
VI	$\frac{Ca\ +}{+\ ti}$ ♂	25	19	29	28	101	56·4 ± 4·9
VII	$\frac{Re\ +}{+\ ti}$ ♂	102	144	36	33	315	20·9 ± 2·2
	$\frac{Re\ ti}{+\ +}$ ♂	3	2	13	21	39	
	$\frac{Re\ +}{+\ ti}$ ♀	79	72	24	19	194	19·5 ± 2·1
	$\frac{Re\ ti}{+\ +}$ ♀	16	8	60	65	149	
IX	$\frac{T\ +}{+\ ti}$ ♂	24	25	30	22	101	51·5 ± 5·0
XI	$\frac{Mi^{wh}\ +}{+\ \ ti}$ ♂	28	29	26	18	101	43·6 ± 4·9

this. Subsequent work by Dickie and colleagues suggests that *Al* is in fact closely linked to *Re*, a figure of 2% recombination between these loci being given by Green & Dickie (1959) in their linkage map of the mouse. Mrs P. W. Lane informs me that latest results from linkage tests now in progress, based on a later final classification for *Al*, give 6·7% recombination between *Re* and *Al*, and 21·7% between *Al* and *sh-2*.

Taken together, the data of Table 2 suggests the following map of linkage group VII (map-distances calculated by means of Kosambi's formula):

Re..7..*Al*....'2....*ti*..3..*Tr*..2..*sh-2*..2..*vt*.....25.....*wa-2*

https://doi.org/10.1017/S0016672300000604 Published online by Cambridge University Press

Table 2. *Data on recombination percentages between loci in linkage group VII (sexes combined)*

Authors	Results
Falconer (1947)	*Re*.....20.....*sh-2*
	Re.....41.....*wa-2*
Snell *et al.* (see Grüneberg, 1952)	*sh-2*.....29.....*wa-2*
Carter (1951)	*Re*.....42.....*wa-2*
Carter & Phillips (1953)	*Re*.....19.....*sh-2*.....24.....*wa-2*
	Re.....44.....*wa-2*
Michie (1952)	*Re*....22....*vt*..2..*sh-2**
Michie (1955)	*vt*.....28.....*wa-2*
Falconer & Sobey (1953)	*Re*....23....*Tr*..3..*sh-2*
Dickie (1955)	*Re*.....33.....*Al*.....39.....*wa-2*
	Al.....28...*sh-2*
	Al.....45...*vt*
Lane (unpublished, 1960)	*Re*.....7.....*Al*.....22...*sh-2*
Searle (this paper)	*Re*.....20...*ti*..9...*vt*.....22.....*wa-2*

* Not known whether *sh-2* lies to right or left of *vt*.

This is similar to the map given by Green & Dickie (1959), though they show the distances in terms of recombination percentages. The close proximity of four genes, three with neurological actions, in the middle of the linkage group is worth noting. As Falconer & Sobey (1953) pointed out, this region may be one of low chiasma frequency. The exact order of these four loci is still not known for certain, though that given seems the most probable one. It might also be noted that Kosambi's formula, when applied to recombination percentages between distant loci, seems here to lead to an overestimate of map-distance. Thus estimates based on the *Re–wa-2* recombination frequencies alone would suggest these loci are over 60 map units apart, which is much higher than that obtained when intermediate loci are used.

In its behaviour, the tipsy mouse has some anomalous features in common with other mutants showing locomotor instability, but closely resembles none of them. Allelism with these mutants is generally ruled out by linkage relationships. Reeler (Falconer, 1951) and waddler (Yoon, 1959) mice sway and sometimes fall over, but the hindquarters are affected rather than the fore-parts of the body. Reelers, moreover, are sterile and show signs of mental deficiency. Ducky (Snell, 1955), vacillans (Sirlin, 1956) and agitans (Hoecker *et al.*, 1954) mice all tend to sway and fall over too, but they have a duck-like waddling gait different from the rabbit-like locomotion of tipsy. In ataxia (Lyon, 1955), Wabbler-lethal (Dickie *et al.*, 1952) and quivering (Yoon & Les, 1957) the effects on locomotion are much more severe than in tipsy, the mice becoming more or less completely helpless, with early death.

SUMMARY

Tipsy (symbol *ti*) is a fully penetrant recessive mutant in linkage group VII of the mouse. Homozygotes have a peculiar rabbit-like gait from the age of a week,

followed soon after by a tendency for the fore-part of the body to sway from side to side, leading to a reeling locomotion with falling over in severely affected mice. There is marked variation in manifestation and some amelioration in older animals; both sexes are fertile.

Linkage relationships in group VII are discussed and tipsy is compared with other mutants showing locomotor instability.

Data on tipsy's linkage relationships, etc., were collected by Miss Anne Constantine for Dr T. C. Carter, who later handed the material over to me. I am very grateful to both of them. I am also grateful to Dr Mary Lyon for suggesting improvements to the manuscript, and to Mrs Priscilla Lane for allowing me to refer to her unpublished linkage data.

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