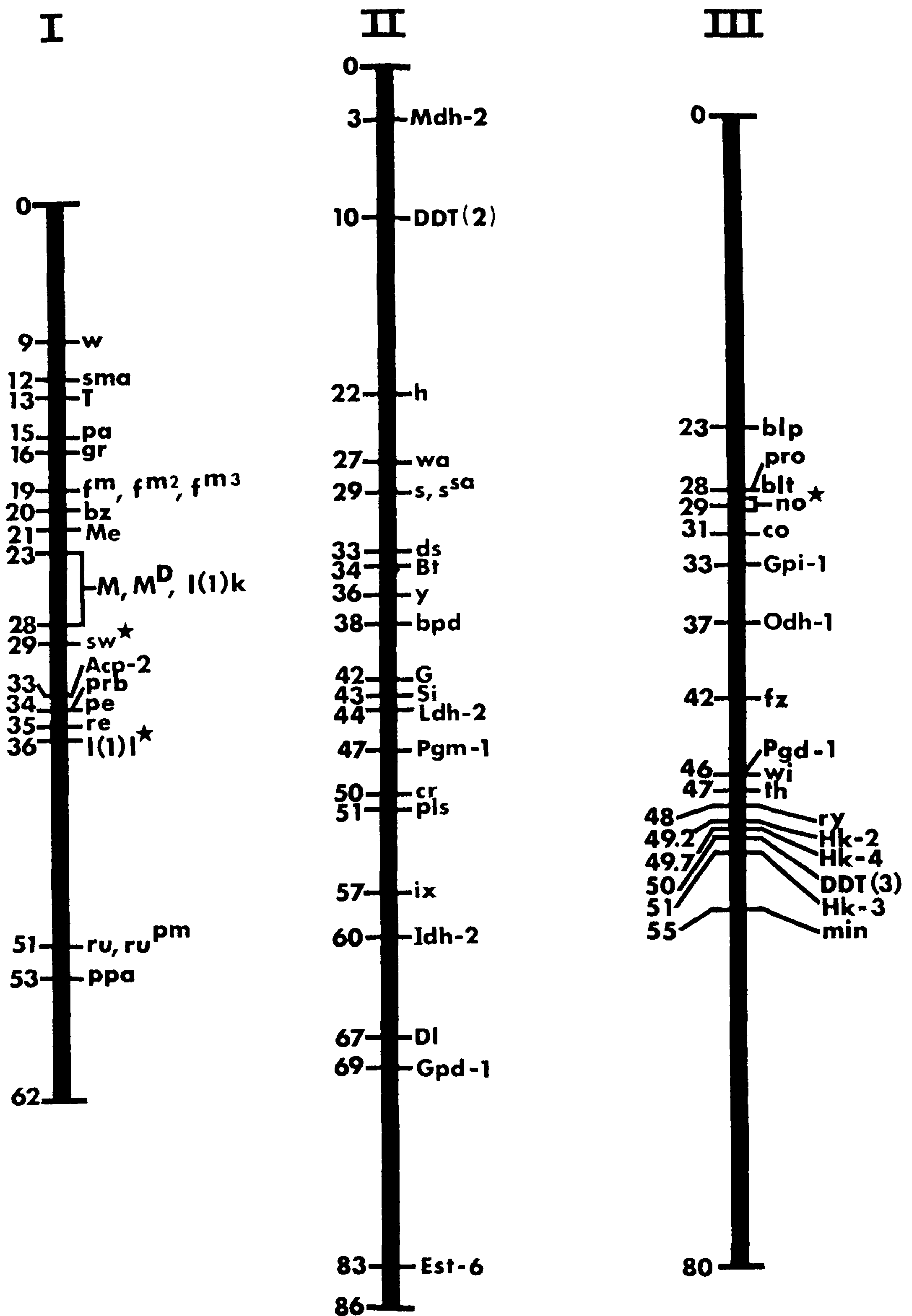

FIGURE 1—Linkage map of *Aedes aegypti*. The total length of the linkage map was calculated from observed chiasma frequencies, while the length of each linkage group corresponds to the physical length of the chromosome. For the starred loci (*sw* and *l(1)l*) in group I, the direction from *sex* was unspecified; in group III, the *no* locus is a physical marker whose position is approximated from *blt*.

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Genetics of *Aedes aegypti*

Updating the linkage map

LEONARD E. MUNSTERMANN AND GEORGE B. CRAIG, JR.

IN HIS SURVEY of mosquito genetics literature in 1953, J.B. Kitzmiller was able to discover only 12 papers dealing with formal genetics[29], none of them focusing on *Aedes aegypti*. By 1960 there was still little information available as Christophers stated that "No mutant forms appear to have been described in *Aedes aegypti*"[11]. However, Mattingly[36,37] had discussed the probable genetic basis of the high degree of phenotypic variation existing among populations of this dread disease vector and thus provided the necessary spark for the discovery of mutants and genetic mapping carried out shortly thereafter by Craig[16,17,65] and McClelland[38,39]. In the 1967 Craig and Hickey review[15], 87 mutations were described, and 28 loci assigned to the three linkage groups for a map distance totaling 110 units. Later, a more detailed mapping study of the known sex-linked morphological markers was provided[6].

In the following decade, the many additional advances made in the genetics of *Ae. aegypti* have been well documented in the reviews of Rai and Hartberg[53] and Kitzmiller[30]. Contributions to the formal genetics subsequent to these reviews have included mapping of factors for recessive lethality[71], susceptibility to parasites[13,60], sex-ratio distortion[47], as well as morphological markers[50,64]. Several additional enzyme loci have been mapped, including three hexokinases[56] and a malic enzyme[57].

Revision of the linkage map for *Ae. aegypti* was deemed necessary for the following reasons. First, it is apparent from the above that many additions must be made in Craig and Hickey's map. Second, a number of cytological observations concerning chiasmata frequency[66] and translocation breakpoints[21] as well as the association of chromosome pairs with the linkage groups[40] have made possible the provision of a map that more fully takes into consideration the physical structure and behavior of the chromosomes. Third, in the past five years, information on several additional morphological and enzyme loci has been accumulated in our laboratory.

Methods

In constructing the new linkage map, nomenclature for morphological marker loci and alleles followed the guidelines established in *Drosophilia* genetics[42]. The names, numbers, and abbreviations for enzymes were those recommended by the Commission of Biochemical Nomenclature[14]. The enzyme loci were numbered consecutively in the order of electrophoretic migration rates from the gel origin. Where only one locus of activity was observed, the number "one" was assigned to the locus for nomenclatural consistency.

Construction of the linkage map was based on two premises. First, chiasmata frequencies were equated with crossover rates according to the 'chiasmatype' theory, and second, chiasma frequency per chromosome was considered proportional to its length[68]. A maximum map length was calculated by multiplying the average number of chiasmata per cell by 50, on the assumption that rates of crossover and chiasmata were equivalent[68]. Hybrid males of a multiple marker and wild-type strain cross had been found to have an average of 1.52 chiasmata per bivalent in meiosis[66]. According to the chiasmatype theory, this should be sufficient to produce a total crossover map distance of 228 map units:

$$\frac{1.52 \times 3 \text{ bivalents } (\times 100)}{2 \text{ chiasmata chromatids/tetrad}}.$$

The chiasmata were assumed to be distributed proportionally to the chromosome length (chr. 1 = 0.27; chr. 2 = 0.38; chr. 3 = 0.35)[40,52], so that the expected map lengths became approximately 62, 86, and 80 units, respectively. The maps obtained by experimental crossing data were then centered on the theoretical map lengths. In the cases where several values for a crossover distance between two markers were reported, either an average or a most common value was used.

Discussion and New Linkage Information

The importance of constructing linkage maps in economically important insects has often been mentioned[15,30], and with the more recent development of enzyme locus mapping technique it has become feasible to detect interspecific chromosome homologies. The genes coding for soluble enzymes now commonly used for population genetics analysis apparently exist in the genome in single copies[31]. These genes did not come into existence de novo during speciation, but have been retained over a long evolutionary period with little functional change[19].

Among culicine mosquitoes, only the salivary polytene chromosomes of *Culex pipiens* have been found to be of sufficient quality for mapping[61,62]. Because of the homo-

The authors are, respectively, postdoctoral research associate, and director of the Vector Biology laboratory, Department of Biology, University of Notre Dame, Notre Dame IN 46556. This work is supported by NIH Training Grant AI-00400 and NIH Research Grant AI-02753.

geneity of metaphase karyotypes among the aedine species, the suggestion has been made that evolution in this group has proceeded by point mutation rather than chromosomal "repatterning"[52]. The mapping of enzyme loci in *Aedes aegypti* and in two *Culex* species can be used to locate the possible presence of repatterning events.

Table I shows where loci have been placed in linkage groups in the three culicine species most thoroughly studied from a genetic standpoint. An intriguing feature of the comparison is that if linkage groups II and III in *Culex pipiens* were switched, seven of eight loci correspond to linkage groups established for *Aedes aegypti*. Further similar comparisons will result in a more uniform nomenclature for chromosomes and linkage groups in the establishment of linkage maps of homologous loci among species.

The linkage map

Linkage information available from enzyme studies, previously unpublished data, and a literature survey, provided the basis for a detailed linkage map of *Aedes aegypti* (Figure 1). Sixty genetic markers (Table II) were associated with the three linkage groups, over a genetic map totaling 156 units. Linkage group I has 22 markers assigned for a map spanning 44 units; group II has 21 markers spanning 80 units; group III has 17 markers spanning 32 units. The markers were classed as morphological (35), enzyme (14), physiological (9), or lethal (2).

Included in Figure 1 were five morphological and nine biochemical markers not previously described. A brief description of each follows.

Morphological loci

Cream-eye (*cr*); linkage group II. Data from J.M. Lichtenfels and G.B. Craig. The mutant was discovered by W.L. Kilama in a West African strain of the *formosus* subspecies. The mutant eye lacks pigment in the larval and pupal stages, and the creamy-gray coloration persists without darkening in the adult. This was found to be an excellent marker with clear expression and complete penetrance.

Prolapsis (*pro*); group III. Data from D.B. Taylor and G.B. Craig. The mutant was discovered by C.E. Machado-Allison, Central University of Caracas. The homozygous mutant is expressed in the larval stage as a continuous outgrowth of the peritrophic membrane to a length often exceeding that of the larva. The expression is best in fourth instar larvae and responds well to selection, although penetrance is incomplete. Genetic crosses indicate close linkage with black-tarsus (*blt*). Larval mortality in selected stocks is greater due to entanglement with the outgrowth.

Plum-eye (ru^{pm}); group I. Data from A.M. Berges and G.B. Craig. The eye is a purple-brown color, darker than rust-eye, but distinct from wild type. It is allelic to rust-eye; expression is good and penetrance is complete.

Rosy-eye (*ry*); group III. Data from J.L. Petersen and G.B. Craig. The mutant was discovered by R.P. McDonald. The eye is pink to rose-colored and darkens progressively with age in the adult. It is expressed only in individuals homozygous for white-eye in linkage group I (epistatic to white-eye). Rosy-eye is linked to black-tarsus (*blt*) with a crossover distance of 20 units between them.

Sable-scale (s^{sa}); group II. Observations of R.P. McDonald and G.B. Craig. In homozygotes, all silver scales are affected, appearing soot-covered and blackened. It is allelic to spot-abdomen(*s*). This mutant is an excellent marker with consistant expressivity and complete penetrance.

Enzyme loci

The phenotypes of these loci are described as they appeared after electrophoresis, using polyacrylamide gels and appropriately stained. Alleles were distinguished by differential electrophoretic mobility, and analyses of allele frequencies have been carried out in African populations of *Aedes aegypti*[43,58,59]. Details of electrophoretic technique and genetic data are available as well[43].

Acid phosphatase (*Acp-2*; E.C. 3.1.3.2); group I. Differ-

Table I. Linkage associations of enzyme loci in three of the most studied culicine mosquito species

Species	Linkage group				
	I	II	II*	III†	III
Aedes aegypti	*Acp-2* (43)‡ *Me-3* (57)	*Idh-2* (43) *Ldh-2* (43) *Mdh-2* (43)	*EST-6* (43,63) *GPD-1* (43) *PGM-2* (8,43)	*Gpi-1* (43) *Hk-2,3,4* (56) *Odh-1* (43)	*Pgd-1* (43)
Culex pipiens	*Lap-1* (48) *Lap-1* (7)		*Gpi* (10) *Hk* (10) *Adh* (45)	*EST-1* (18,44) *EST-2* (10) *PGM* (9) *GPD* (49)	*Pgd* (9)
Culex tritaeniorhynchus	*Amy* (1) *Idh* (1)	*Ldh* (1) *Aph* (1)			*Adh* (1)

* Compare with markers in starred linkage group III
† Compare with markers in starred linkage group II
(Note: Some loci were capitalized for ease in comparison)
‡ Numbers in parentheses refer to literature citations

ent alleles vary in strength of expression in response to the 1-napththol acid phosphate substrate used. Heterozygotes have somewhat indistinct banding, and are intermediate in migration to the parental bands. Clearest expression occurs in pupae and teneral adults.

Glycerol 3-phosphate dehydrogenase (*Gpd-1;* E.C. 1.1.1.8); group II. Banding phenotype appears in response to glycerol 3-phosphate substrate as a single band in inbred homozygotes and distinct triple bands in hybrid heterozygotes. In the latter, the two fainter bands migrate at the same rate as the two parentals with a denser band intermediate between them. In backcross progeny, a 1:1 ratio of triple-banded heterozygote to single-banded homozygote phenotypes occur, indicating a genetic basis for a dimeric enzyme structure. Clearest expression occurs in adults. Three alleles are discernible, but only one is commonly seen.

Glucosephosphate isomerase (*Gpi-1;* E.C. 5.3.1.9); group III. The substrate used was fructose 6-phosphate, with distinct parental and hybrid phenotypes as described for *Gpd-1*. Clearest banding occurs in adults; five alleles are found, usually in strains collected from sylvan habitats.

Isocitrate dehydrogenase (*Idh-2;* E.C. 1.1.1.42); group II. Findings corroborated by unpublished data of W.J. Tabachnick and J.M. Lichtenfels. The substrate is sodium

Table II. Mutants of *Aedes aegypti* named and mapped to three linkage groups, with references since 1967; asterisks in reference column indicate information presented in the text.

No.	Symbol	Mutant name	Group	References
1	*Acp-2*	Acid phosphatase-2	I	43,*
2	*blp*	black-palp	III	3,15,26,41,56
3	*blt*	black-tarsus	III	4,15,21,25,26 35,40,42,64a, 67,69
4	*bpd*	black-pedicel	II	12,15,41
5	*Bt*	Black-tergite	II	34,50
6	*bz*	bronze-cuticle	I	3–6,20–22,41
7	*co*	compressed-antenna	III	15,26,56
8	*cr*	cream-eye	II	*
9	*Dl*	Dieldrin-resistance	II	15,27,28,33
10	*DDT* (*2*)	DDT-resistance	II	12,15,27,33,35
11	*DDT* (*3*)	DDT-resistance	III	26,35,69
12	*ds*	dark-scutum	II	3,15,27
13	*Est-6*	Esterase-6	II	43,55,63
14	f^{m}	filarial suscepti-bility, *Brugia malayi*	I	15,60,72
15	f^{m2}	filarial suscepti-bility, *Waltonella* (=*Foleyella*) *flexicauda*	I	60
16	f^{m3}	filarial suscepti-bility, *Dirofilaria repens*	I	13
17	*fz*	fuzzy-scale	III	3,15,26,41,56
18	*G*	Gold-mesonotum	II	15
19	*gr*	grey-body	I	15
20	*Gpd-1*	Glycerol-3-phos-phate dehydro-genase-1	II	43,*
21	*Gpi-1*	Glucosephosphate isomerase-1	III	43,*
22	*h*	halteres	II	15,27
23	*Hk-2*	Hexokinase-2	III	56
24	*Hk-3*	Hexokinase-3	III	56
25	*Hk-4*	Hexokinase-4	III	56
26	*Idh-2*	Isocitrate dehydrogenase-2	II	43,*
27	*ix*	intersex	II	15
28	*l* (*l*) *k*	lethal	I	71
29	*l* (*l*) *l*	lethal	I	71
30	*Ldh-2*	Lactate dehydrogenase-2	II	43,*
31	*m, M*	sex	I	2–6,15,20,22, 40–42,46, 47,54,57,60, 64,71
32	M^{D}	Distorter, sex-ratio	I	15,24,46,47
33	*Mdh-2*	Malate dehydro-genase-2	II	43,*
34	*Me*	Malic-enzyme	I	57
35	*min*	miniature-body	III	3,15,26,41,56, 65,67
36	*no*	nucleolar-organizer	III	4,21,40,67
37	*Odh-1*	Octanol dehydro-genase-1	III	43,*
38	*pa*	pale-abdomen	I	15
39	*pe*	palp-extended	I	22,54
40	*Pgd-1*	Phosphogluconate dehydrogenase-1	III	43,*
41	*Pgm-1*	Phosphogluco-mutase-1	II	8,43,*
42	*pls*	plasmodium susceptibility	II	15,28
43	*ppa*	palp-antenna	I	51
44	*prb*	proboscipedia	I	22,54
45	*pro*	prolapsis	III	*
46	*re*	red-eye	I	3,4,6,15,23, 39–41, 51,54,57,64a
47	*ru*	rust-eye	I	3,6,15,39,41, 51,54
48	ru^{pm}	plum-eye	I	*
49	*ry*	rosy-eye	I	*
50	*s*	spot-abdomen	II	3,4,12,13,15, 21,25,27,33, 41,42,55,63, 69
51	s^{sa}	sable-scale	II	*
52	*Si*	Silver-mesonotum	II	15,21,28,33, 41,42,64a
53	*sma*	small-antenna	I	20,54
54	*sw*	short-wing	I	64
55	*T*	Terminalia	I	15,23
56	*th*	tarsi-hooked	III	15
57	*w*	white-eye	I	2–6,15,21,22, 41,42,51,60, 65
58	*wa*	wart-palp	II	15,27
59	*wi*	withered-leg	III	15
60	*y*	yellow-larva	II	8,15,27,33,55, 63,69,70

isocitrate; inbred and hybrid phenotypes are similar to those of *Gpd-1*. Two alleles are commonly found. There is clear expression of bands in both pupae and adults.

Lactate dehydrogenase (*Ldh-2;* E.C. 1.1.1.27); group II. The substrate is lactate acid. In inbred lines, the homozygote usually is characterized by a dense band immediately preceded by a lighter staining band. In the hybrid, a broad diffuse band of intermediate migration appears midway between the parental controls. Good expression occurs only in pupal and teneral adult stages.

Malate dehydrogenase (*Mdh-2;* E.C. 1.1.1.37); group II. With malic acid as the substrate, the banding phenotypes are similar to those of *Gpd-1*. Three alleles are commonly found; expression is clearest in adult mosquitoes.

Octanol dehydrogenase (*Odh-1;* E.C. 1.1.1.73); group III. Although octanol is the commonly used substrate, other similar alcohols (such as butanol) produces identical phenotypes. The banding of inbred lines and hybrids is similar to *Gpd-1*, but the banding is less clear being somewhat obscured by 'tetrazolium oxidase' activity. Two alleles can be distinguished—a slow allele in domestic, man-associated populations, and a fast allele confined to sylvan populations. Expression is best in pupae and teneral adults.

Phosphogluconate dehydrogenase (*Pgd-1;* E.C. 1.1.1.44); group III. The bands appear in response to 6-phosphogluconic acid substrate. The patterns are similar to those of *Gpd-1;* however, each major band has an immediately antecedent lighter band. These lighter bands are associated with all bands of both homozygotes and heterozygotes, indicating an epigenetic origin. Five alleles are commonly found in sylvan populations. Expression is best in newly emerged adults.

Phosphoglucomutase (*Pgm-1;* E.C. 2.7.5.1); group II. Description of phenotypes and initial mapping was carried out by Bullini, et al.[8] Additional mapping with several crosses confirmed their findings and fixed the locus relative to spot-abdomen, yellow-larva and three other enzyme markers.

Additional considerations

A few changes were necessary in the map of Craig and Hickey[15]. One important error was the placement of the gene for larval resistance to DDT. Coker, in 1966 found that this gene was located on the *far* side from Dieldrin-resistance, across the spot-abdomen marker[12]. This was later confirmed independently[33].

The linkage map model (Figure 1) based on chiasma frequency and chromosome length illuminates details of marker distribution and provides a base for further investigation of chromosomal behavior. However, the markers are not distributed evenly over the map. In linkage group III, the 17 markers are clumped in a 44-unit map while the model predicts an 80-unit map. This implies that 1) markers have not yet been found that delimit the ends of linkage group III, or 2) chiasmata occur in this chromosome at a rate lower than the model predicts. Nevertheless, the linkage associations of markers in Figure 1 are probably correct, since most have been tested for linkage several times. However, the placement of some loci relative to one another in a given group may not be correct. The sources of such error are several: 1) since all markers were not tested relative to one another, and, given the degree of crossover variability between crosses from one cross to the next[15], closely linked markers not tested in the same backcross may not have been ordered correctly; 2) when single-pair crosses and controlled rearing procedures are not used, or if markers are not fully penetrant or difficult to score, exaggerated crossover values may be obtained[15,27]; 3) when loci are on opposite arms of a chromosome and double crossovers cannot be scored, the distance will be underestimated[43,55,83]; 4) great differences in crossovers between given markers from one strain to the next have been observed, due possibly to the presence of inversions or other factors interfering with crossover rates[43].

Therefore, changes in the gene order presented here will certainly be found, although this arrangement is as correct as data from the literature and personal observation presently allow.

Summary

A new linkage map for *Aedes aegypti* was constructed with a total of 60 markers. Thirty-two have been added to the previously published 12-year-old map. Brief descriptions are provided for five morphological and nine enzyme markers not previously published. The markers span a total map distance of 156 units: linkage group I—17 loci (22 markers) spanning 44 units; linkage group II—20 loci (21 markers) spanning 80 units; linkage group III—17 loci spanning 32 units.

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