Chromosomal localization of lipolytic enzymes in the mouse: pancreatic lipase, colipase, hormone-sensitive lipase, hepatic lipase, and carboxyl ester lipase

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Abstract Several lipases and their cofactors are involved in the absorption, transport, storage, and mobilization of lipids. As part of an effort to examine the role of these enzymes in plasma lipid metabolism and genetic susceptibility to atherosclerosis, we report the chromosomal mapping of their genes in mouse. Restriction fragment length variants for each gene were identified, typed in an interspecific cross, and tested for linkage to known chromosomal markers. The gene for pancreatic lipase resides on chromosome 19, while the gene for its cofactor, colipase, is on chromosome 17. A gene for a protein with sequence similarity to pancreatic lipase was tightly linked (no observed recombination) to the gene for pancreatic lipase, suggesting a gene cluster. The gene for hormone-sensitive lipase is near the gene cluster containing apolipoproteins C-II and E on chromosome 7. The gene for hepatic lipase is near the gene for apolipoprotein A-I on chromosome 9. The carboxyl ester lipase gene resides on chromosome 2. Previously, we have mapped the gene for lipoprotein lipase to chromosome 8. Thus, with the exception of pancreatic lipase and a related protein, these lipase genes, including several that are members of a gene family, are widely dispersed in the genome. Comparison of chromosomal locations for these genes in mouse and humans shows that the previously observed interspecies syntenies are preserved.—**Warden, C. H., R. C. Davis, M-Y. Yoon, D. Y. Hui, K. Svenson, Y-R. Xia, A. Diep, K-Y. He, and A. J. Lusis.** Chromosomal localization of lipolytic enzymes in the mouse: pancreatic lipase, colipase, hormone-sensitive lipase, hepatic lipase, and carboxyl ester lipase. *J. Lipid Res.* 1993. **34:** 1451–1455.

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The absorption, transport, storage, and mobilization of lipids is mediated, in part, by various lipases (reviewed in 1, 2). Thus, pancreatic lipase and its cofactor, colipase, are primarily responsible for duodenal hydrolysis of dietary triglycerides (TG). Carboxyl ester lipase, another gastrointestinal lipase, is relatively nonspecific and is thought to mediate hydrolysis of vitamin esters and cholesteryl esters. The lipolysis of plasma lipoproteins is mediated by lipoprotein lipase and hepatic lipase. Lipoprotein lipase is responsible for the hydrolysis of core TG in chylomicrons and very low density lipoproteins, while hepatic lipase functions in the conversion of intermediate density lipoproteins to low density lipoproteins and possibly, in the interconversion of high density lipoprotein subtypes. Lipoprotein lipase activity is strongly enhanced by its cofactor apolipoprotein C-II (apoC-II), while hepatic lipase has no cofactor requirements. Pancreatic lipase, lipoprotein lipase, and hepatic lipase are all members of a gene family derived from a common ancestral sequence (3). Hormone-sensitive lipase plays a pivotal role in the mobilization of free fatty acids from adipose tissue by controlling the rate of lipolysis of stored TG (4). Mutations of some of these lipases are responsible for certain rare disorders of lipid absorption and lipoprotein metabolism (reviewed in 2). Thus, type I hyperlipidemia, characterized by very high plasma TG levels and chylomicron accumulation, results from rare genetic deficiencies of lipoprotein lipase or apoC-II (2). It is also likely that less drastic alterations in the expression

Abbreviations: CEL, carboxyl ester lipase; HL, hepatic lipase; HSL, hormone-sensitive lipase; apoC-II, apolipoprotein C-II; hPL, human pancreatic lipase; hPLRP, human pancreatic lipase-related protein; RFLV, restriction fragment length variants; TG, triglycerides; HDL, high density lipoprotein.

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of lipase genes are responsible, in part, for individual variations of plasma lipoproteins, obesity, and other risk factors contributing to atherosclerotic artery disease (2). However, the analysis of such complex traits is difficult in humans due to genetic heterogeneity, environmental influences, and other complications (5). Therefore, we are utilizing a mouse animal model to examine the potential role of lipases and other "candidate genes" in the genetic control of these traits. Genetic studies with inbred animal models avoid the problems of genetic heterogeneity and environmental influences, and a number of genetic loci contributing to lipid metabolism or early atherosclerosis have been identified in rodents (5). As part of this effort, we report here the chromosomal mapping of the above lipases in the mouse.

MATERIALS AND METHODS

C57BL/6J mice were purchased from the Jackson Laboratory, Bar Harbor, ME. *Mus spretus* were a gift from Dr. Michael Potter, National Institutes of Health. C57BL/6J and *M. spretus* parental strains were mated and offspring were backcrossed to the C57BL/6J parent line to construct a set of interspecific backcross mice (6). Genomic DNA from parental and F1 mice was digested with several restriction enzymes (*Bam*HI, *Bgl*II, *Eco*RI, *Hind*III, *Msp*I, *Pst*I, *Pvu*II, *Sst*I, *Taq*I, and *Xba*I) and analyzed by Southern hybridization to determine informative restriction fragment length variants (RFLV) using cDNA probes for rat carboxyl ester lipase (CEL) (7), rat hormone-sensitive lipase (HSL) (4), rat hepatic lipase (HL) (8), human colipase (9), human pancreatic lipase (hPL) (10), and hPLRP1, a human pancreatic lipase-related protein (10, 11). The hPL and hPLRP probes were generously provided by Hofmann LaRoche, Basel. Linkage was determined by examining the segregation of *M. spretus* alleles in the set of backcross mice and comparison with the segregation patterns of previously typed genetic markers. Thus, markers closely linked to the lipase genes were identified by low recombination frequencies. The linked markers included cDNAs typed by RFLV: *Acra,* the acetylcholine receptor alpha chain (12); *Pgs-1,* the constitutive prostaglandin synthase/cyclooxygenase (6, 13); *Pim-1,* a proviral integration site (14), *Apoe,* apolipoprotein E (15), and *Apoa1,* apolipoprotein A-I. The probe for *Apoa1* was isolated as a random mouse liver cDNA and identified by sequence comparison to the published rat cDNA sequence (data not shown). Microsatellite markers *D2Mit1* (*D11S14h*), *D7Mit20, D9Mit8, D17Mit18, D17Nds3, D19Mit1,* and *D19Mit4* (16) were typed by polymerase chain reaction. The $\log_{10}$ (likelihood of linkage/likelihood of no linkage) (LOD) scores for two-point linkage (17) and the most probable order of markers on each mouse chromosome were calculated using the MAPMAKER program (18) generously provided by S. Lincoln and E. Lander, MIT, Cambridge, MA.

RESULTS

Lipase cDNA probes were used to identify restriction fragment length variants between *M. spretus* and C57BL/6J (**Table 1**). Segregation of these polymorphisms was determined in a set of 67 interspecific backcross mice and compared with the segregation of about 250 previously typed polymorphic chromosomal markers spanning nearly the entire mouse genome (unpublished). Lipase chromosomal mapping assignments, based on recombination with markers, are shown in **Table 2.** For each lipase probe, linkage was established with two previously mapped markers on the same mouse chromosome. Table 2 shows the recombination frequency (± standard error, SE) between markers and the lipase probe. In every case, the lipase probe showed a two-point linkage LOD score of 11.0 or more for the nearest marker. For linkage to the more distant marker, the LOD score was at least 5.0. Thus, each lipase probe shows very strong linkage to at least two previously mapped mouse genes. No strong linkages were observed to markers on other chromosomes. In

TABLE 1. Lipase restriction fragment length variants

Probe	Restriction Enzyme	Fragment Size (kilobases)	
		C57BL/6J	Spretus[a]
Carboxyl ester lipase	*Pst*I	4.4, 2.9, 0.7	2.9, 1.9, 0.7
Hormone-sensitive lipase	*Pst*I	3.0, 2.0, 1.6	4.8
Hepatic lipase	*Pst*I	3.9, 2.6, 1.6	3.2, 2.6, 1.6
Colipase	*Hind*III	5.6	7.6
Pancreatic lipase	*Eco*RI	2.4	2.3
Pancreatic lipase-related protein	*Hind*III	3.8	3.3

[a] Underlined fragment was used to score segregation of *M. spretus* alleles in backcross mice.

TABLE 2. Mouse lipase linkage map

Marker 1	Marker 2	% Recombination ± S.E.	L.O.D. Score
Chromosome 2			
D2Mit1	*Cel*	19 ± 5	5.0
Cel	*Pgs-1*	6 ± 3	13.3
Pgs-1	*Acra*	16 ± 5	7.2
Chromosome 7			
Apoe	*Lipe*	2 ± 1	17.9
Lipe	*D7Mit20*	2 ± 1	17.0
Chromosome 9			
Apoa1	*Lipc*	15 ± 4	7.9
Lipc	*D9Mit8*	6 ± 3	11.0
Chromosome 17			
D17Mit18	*Pim-1*	12 ± 4	9.3
Pim-1	*Clps*	2 ± 1	17.9
Clps	*D17Nds3*	9 ± 4	10.3
Chromosome 19			
Pnlip	*Plrp-1*	0 ± 0	20.2
Plrp-1	*D19Mit4*	6 ± 3	12.5
D19Mit4	*D19Mit1*	6 ± 3	12.5

The linkage of lipase genes to mapped markers is presented with the most proximal markers (relative to the centromere) listed first. Markers were scored in a total of 67 (C57BL/6J × *M. spretus*) F1 × C57BL/6J backcross mice.

order to determine the most likely order of lipase and marker genes on each chromosome, a maximum likelihood map was calculated using the MAPMAKER program (18). The order of lipases and previously mapped markers is shown in Table 2 with the centromere at the top of the list and telomere at the bottom.

The results (Table 2) indicate that the gene for carboxyl ester lipase, designated *Cel,* is located on chromosome 2, 6 ± 3 centimorgans (cM) proximal (relative to the centromere) to the gene for the constitutive form of prostaglandin synthase (*Pgs-1*). The gene for hormone-sensitive lipase, designated *Lipe* resides on chromosome 7, 2 ± 1 cM distal to the gene for apolipoprotein E (*Apoe*). The gene for hepatic lipase, designated *Lipc,* resides on chromosome 9, 15 ± 4 cM distal to the gene for apolipoprotein A-I (*Apoa1*) and 6 ± 3 cM proximal to the microsatellite marker *D9Mit8.* The gene for colipase, designated *Clps,* resides on chromosome 17, 2 ± 1 cM distal to the proviral integration site marker *Pim-1.* The gene for pancreatic lipase, designated *Pnlip,* and a pancreatic lipase-related protein, designated *Plrp-1,* exhibited no recombination, indicating that they may be part of a gene cluster. Both reside on chromosome 19, 6 ± 3 cM proximal to the microsatellite marker *D19Mit4.* In designating gene symbols for the mouse, we have attempted to conform to the corresponding human gene symbols.

DISCUSSION

We have determined the chromosomal organization of the genes for six lipases in the mouse. Previously, we mapped the gene for lipoprotein lipase, designated Lpl, to the proximal region of mouse chromosome 8 (15). These results clarify the evolutionary relationships of the lipases, provide new markers for genetic studies, and add to the understanding of mouse–human syntenic relationships. Most importantly, the information will be useful for analysis of genetic factors contributing to mammalian lipid metabolism.

Pancreatic lipase, pancreatic lipase-related protein, hepatic lipase, and lipoprotein lipase are members of a gene family derived from a common ancestral sequence (3, 11). They exhibit significant sequence similarity and resemble one another in gene organization. Our results indicate that the genes for pancreatic lipase and pancreatic lipase-related protein are tightly linked on mouse chromosome 19, suggesting a gene cluster resulting from duplication of an ancestral gene. Interestingly, the map position for pancreatic lipase and pancreatic lipase-related protein is close to *Es-18,* a locus defining variation in a nonspecific esterase. Further mapping and sequence data will be required to determine whether *Es-18* is clustered with or evolutionarily related to pancreatic lipase. On the other hand, lipoprotein lipase and hepatic lipase are unlinked to each other or to the pancreatic lipases, indicating that they have been dispersed after duplication of ancestral genes. The remaining lipases, carboxyl ester lipase and hormone-sensitive lipase, as well as colipase and apolipoprotein C-II, exhibit no obvious sequence similarities.

These lipases have previously been mapped in humans by analysis of somatic cell hybrids and in situ hybridization to metaphase chromosomes. **Table 3** lists the analogous chromosomal assignments, in mouse and humans, for each lipase gene. The mouse gene symbol shown is identical to the analogous human gene symbol with the exception that the human symbols are conventionally all capital letters. The approximate map positions for the mouse genes (shown in parentheses next to the chromosome number) were calculated by interpolation between positions of marker genes as listed in the GBASE database of The Jackson Laboratory. Thus, the mouse gene for hormone-sensitive lipase (*Lipe*) is positioned approximately 8 cM from the centromere since the flanking marker genes, *Apoe* and *D7Mit20* (Table 2) are mapped at about 6 and 9 cM, respectively. Map positions for the corresponding human genes are given in relationship to giemsa banding patterns. The cited reference in Table 3 describes the mapping in humans.

The human pancreatic lipase gene (designated PNLIP) is on chromosome 10q26 (19). We have also mapped the

TABLE 3. Human-mouse lipase map synteny

Gene	Gene Symbol	Chromosome Map Position		Reference
		Mouse	Human	
Carboxyl ester lipase	*Cel*	2 (20 cM)	9qter	(25)
Hormone-sensitive lipase	*Lipe*	7 (8 cM)	19q13.1	(26)
Apolipoprotein C-II	*Apoc2*	7[a] (6 cM)	19q12-q13.2	(27)
Lipoprotein lipase	*Lpl*	8 (26 cM)	8p22	(28)
Hepatic lipase	*Lipc*	9 (37 cM)	15q21-q23	(28)
Colipase	*Clps*	17 (18 cM)	6p21.1-pter	(9)
Pancreatic lipase	*Pnlip*	19 (30 cM)	10q26	(19)

[a] The *Apoc2* gene is part of a conserved gene cluster with apolipoproteins C-I and E that has been mapped to mouse chromosome 7 (15, 29).

pancreatic lipase-related protein to chromosome 10 by analysis of somatic cell hybrids (Y-R. Xia, R. C. Davis, R. S. Sparkes, A. J. Lusis, unpublished results). Thus, the pancreatic lipase and pancreatic lipase-related protein appear to be clustered in both humans and mouse. In fact, many chromosomal regions contain sets of linked genetic markers conserved between mouse and humans (20, 21). The lipase genes described in this report are located in those conserved regions (Table 3) and, thus, add to the known syntenic relationships between mammalian species.

These results should be useful in the analysis of genetic variations in mice affecting processes related to lipid metabolism. A number of mutants resulting in hyperlipidemia and obesity have been identified and partially characterized in mice (reviewed in 5). From our mapping data, it is clear that mutations to the lipase genes discussed here do not underlie any of the recessive mutations resulting in obesity and diabetes in mice. Thus, the *ob* gene is on chromosome 6, the *db* gene is on chromosome 4, the *fat* gene is on a region of chromosome 8 distinct from that containing *Lpl,* and the *tub* gene is on a region of chromosome 7 distinct from *Lipe* and *Apoc2.* Our results also confirm that the combined lipase deficiency (*cld*) mutation, resulting in the absence of hepatic lipase and lipoprotein lipase activity, is due to a transacting effect on lipase production. Thus, whereas the *cld* mutation maps to mouse chromosome 17, the genes for hepatic lipase and lipoprotein lipase reside on chromosomes 9 and 8, respectively. A similar analysis is possible for the fatty liver dystrophy (*fld*) gene, although the map position for that mutation has not yet been published. The suppression of lipoprotein lipase and hepatic lipase expression in newborn *fld* mice is, most probably, the result of a factor affecting lipase expression in trans, as the two lipase genes are found on separate chromosomes.

While the lipase genes do not underlie the above recessive mutations resulting in extreme alterations of lipid metabolism, subtle alterations in expression of lipase genes could well contribute to the genetic differences in plasma lipoproteins, fat accumulation, or early atherosclerosis that occur among inbred strains of mice (reviewed in 22, 23). Two genetic loci contributing to HDL cholesterol levels and aortic fatty streak development, designated *Ath-1* and *Ath-2,* have been identified (22). *Ath-1* has tentatively been assigned to the distal region of mouse chromosome 1 and does not correspond to any of the gene loci reported here. The application of quantitative trait locus mapping is likely to reveal additional loci contributing to complex traits involving lipid metabolism (23). As genetic alterations in the expression of certain lipases, including lipoprotein lipase (24) and hepatic lipase (Imes, S., Doolittle, M. and Lusis, A. J., unpublished results), are known to occur among inbred strains, knowledge of the chromosomal organization of the lipase genes for lipases will be of interest in establishing their possible effects on lipoprotein metabolism.

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