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Mouse Chromosome 12

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The goal of the first of these reports was to assemble markers of Chromosome (Chr) 12 that had been particularly extensively studied in mapping experiments into a limited set of reference maps. The maps that resulted incorporated data for 48 markers and showed good agreement as to gene order and, in many regions of the chromosome, relative spacing (D'Eustachio 1991). These maps still appear valid: no substantial new bodies of multilocus linkage data have been published, and the individual markers newly described in the past year can be interpolated straightforwardly into the existing framework maps.

The goal of the current report, beyond accounting for these new loci, is to review three areas overlooked earlier. These are the correlation of the genetic and physical maps of the chromosome, discussion of the organization of the *Aat* and *Igh* gene complexes, and a systematic review of markers not previously discussed. The report is organized alphabetically by marker name, with the discussion of genetic vs physical maps at the end. As before, the discussion includes a large proportion of hypothesis and opinion, and is intended to highlight interesting and controversial aspects of the map.

Table 1 lists the currently accepted names of all markers associated with the chromosome in GBASE as of 1 March 1992. In addition, wherever a marker has been discussed in publications under another name, whether or not that name was ever officially accepted, a cross-reference is included under the other name. Map positions are those assigned by GBASE, for simplicity.

Aat (Pre-1), Pre-2 (Spi-2, contrapsin)

These two genes specify the mouse homologs (as defined by sequence studies) of the human serine protease inhibitors α 1-antitrypsin (whose major physiological substrate is neutrophil elastase in the lung) and α 1-antichymotrypsin, respectively. The first mouse protein inhibits elastase, trypsin, and chymotrypsin in vitro, whereas the second shows substantial inhibitory activity against trypsin but none against chymotrypsin (Takahara and Sinohara 1982).

Mouse cDNAs corresponding to each protein have been isolated and sequenced (Hill et al. 1984; Krauter et al. 1986; Sifers et al. 1990; Suzuki et al. 1990). Southern blotting analyses reveal multiple genomic DNA fragments closely homologous to each, which vary in size and number from strain to strain of inbred mice (Hill et al. 1985). While the purified mouse proteins have been shown to have the electrophoretic mobility of prealbumins (Myerowitz et al. 1972; Takahara and Sinohara 1982), identity of the electrophoretically and biochemically defined entities has not been formally proven.

The genetic consequences of this ambiguity are minimal. All *Aat*-related DNA sequences were mapped to Chr 12 by analysis of somatic cell hybrids (D'Eustachio 1984; Krauter et al. 1986) and all RFLVs detected with *Aat* probes have been mapped to a single genetic locus on Chr 12 in multiple studies of recombinant inbred (RI) strains and backcross progenies (for example, Birkenmeier et al. 1988; Blank et al. 1988; D'Eustachio 1984; Hill et al. 1985; Seldin et al. 1989). *Pre-2,* defined electrophoretically, failed to recombine with *Aat* in 282 gametes (Green 1989). As defined by protein and DNA variants, contrapsin cosegregated with *Aat* in 24 of 25 BXD RI strains tested (Hill et al. 1985), confirming the tight linkage of *Aat* and *Pre-2* and weakly supporting the marker order cen–*Aat*–*Pre-2* (see *Cbg,* below, for BXD typing data).

Despite the inability to match DNA sequences unambiguously to biochemical phenotypes, the *Aat*–*Pre-2* complex is clearly genetically compact, precisely mapped, and a rich source of easily scored DNA variants for mapping studies.

Table 1. Locus list for mouse Chr 12.

New	Locus	Gene name	A	M (cM)	T	Method	H. symbol	H. location	Reference
	Aat	alpha-1-antitrypsin	1	49	D,B	I,S,R,L,C	*PI*	14q32.1	12,13,32,42,66,67, 78,100,133,148,161
	Acp-1	acid phosphatase-1		syn	B	S	*ACP1*	2p25	43,46
	Ah	aromatic hydrocarbon responsiveness		13	B	S,R	*AHH*	2pter-q31	24,85,116,131,163
*	*Ahh*	not used - see Ah							
	Akt	thymoma viral proto-oncogene		65	D	R,L	*AKT1*	14q32.32-q32.33	23,152
*	*Akvr-1*	not used - see Fv-4							
	Apob	apoliprotein B		3	D,B	R,L	*APOB*	2p24-p23	83,93,115
*	*Amh-rs4*	anti-Mullerian hormone-related DNA sequence-4		43	D	R			74
*	*asp*	not used - see asp-1							
	asp-1	audiogenic seizure prone-1		15	V	R			110,111,127,145,146
	Bcga	BCG-induced anergy		63	B	R,L			141,142
	bd	bradypneic		33	V	L			156
*	*BRS-8*	not used - see Odc-rs8							
*	*c-Fos*	not used - see Fos							
*	*c-Nmyc*	not used - see Nmyc-1							
	Caa	Ca ATPase activity		8	B	R			127
*	*Cbg*	corticosterone binding globulin		53	D	R	*CBG*	14q31-q32.1	86
*	*ck*	not used - see cpk							
	Ck-3	creatine kinase-3		64	D	R,L	*CKBB*	14q32.3	23
	cpk	congenital polycystic kidneys		6	V	L	*PKD2*	?	28
	Crip	cysteine-rich intestinal protein		65	D	R,L			11,23
*	*DAbI-12*	not used - see D12N1							
*	*D12-#*	not used - see D12Nyu#							
*	*D12J1*	DNA segment, Chr 12, JAX-1		64	D	L			106
*	*D12Leh1*	DNA segment, Chr 12, Lehrach-1		4	D	L			26
	D12Mcg1	DNA segment, Chr 12, Med. Coll. of Georgia-1		17	D	R			24
	D12N1	DNA segment, Chr 12, NIH-1		66	D	R,L			7,23
	D12Nyu1	DNA segment, Chr 12, NYU-1	1	20	D	S,R,L			13,32
	D12Nyu2	DNA segment, Chr 12, NYU-2		6	D	S,R,L			13,32,117
	D12Nyu3	DNA segment, Chr 12, NYU-3		23	D	S,R,L			13,32,50
	D12Nyu4	DNA segment, Chr 12, NYU-4		38	D	S,R,L			13,32
	D12Nyu5	DNA segment, Chr 12, NYU-5		10	D	S,R,L			13,32
	D12Nyu6	DNA segment, Chr 12, NYU-6		syn	D	S,R,L			13
	D12Nyu7	DNA segment, Chr 12, NYU-7		10	D	S,R,L			13
	D12Nyu8	DNA segment, Chr 12, NYU-8		35	D	S,R,L			13
	D12Nyu9	DNA segment, Chr 12, NYU-9		65	D	S,R,L			13,50
	D12Nyu10	DNA segment, Chr 12, NYU-10		10	D	S,R,L			13
	D12Rp54	DNA segment, Chr 12, Roswell Park-54		48	D	R			65
	Eif4e	eukaryotic translation initiation factor 4, epsilon chain		21	D	R			36
*	*Env-39*	not used - see Xmmv-39							
	Es-25	esterase-25		7	B	R,L			29
	Etc-1	probably Mtv-9							
	Fcr	Fc receptor		33	B	L			06
	Fos	FBJ osteosarcoma oncogene	1	35	D	S,R,L	*FOS*	14q24.3	4,12,13,32,42
	Fv-4	Friend virus susceptibility-4		33	D	L			52,53,69,114,118
*	*H(Igh)*	not used - see H-40							
*	*H-17*	histocompatibility-17		syn	V	R			139
*	*H-34*	histocompatibility-34		syn	V	R			139
*	*H-38*	histocompatibility-38		syn	V	R			139
	H-40	histocompatibility-40		52	V	L			45
*	*hsp-3*	not used - see Hsp84-3							
*	*hsp-4*	not used - see Hsp86-1							
	Hsp84-3	heat shock protein, 84 kDa-3		syn	D	S			102
	Hsp86-1	heat shock protein, 86 kDa-1		56	D	S,L	*HSPD1 ?*	103104	
	hyt	hypothyroid		31	V	L,C			08
*	*Ias*	not used - see asp-1							
	Igh-C	immunoglobulin heavy-chain constant region	1	65	D,B	I,S,R,L,C,P	*IGH*	14q32.33	9,12,13,16,23,32,34,42, 62,63,100,104,107,144,147,161
*	*Igh-Bgl*	immunoglobulin heavy chain Bgl		69	D,B	R,L			75,167
*	*Igh-Dex*	immunoglobulin heavy chain Dex		67	D,B	R,L			31,136
*	*Igh-Gte*	immunoglobulin heavy chain Gte		66	D,B	R			71
*	*Igh-Nbp*	immunoglobulin heavy chain Nbp		69	D,B	R,L			75,167
*	*Igh-Np*	immunoglobulin heavy chain Np		69	D,B	R,L			75,167
*	*Igh-Ns2*	immunoglobulin heavy chain Ns2		73	D,B	R,L			130
*	*Igh-Sa2*	immunoglobulin heavy chain Sa2		66	B	R,L			75,167
*	*Igh-Sa4*	immunoglobulin heavy chain Sa4		68	B	R,L			75,167
*	*Igh-Src*	immunoglobulin heavy chain Src		73	B	R,L			75,167
*	*Ifi12*	interferon activated gene-12		syn	D	S			120
*	*In*	not used - see Ah							
	iv	situs inversus viscerum		63	D,V	L			20,58,94,150
	ja	allele of Spnb-1							
*	*Lamb-1*	not used - see Lamb1-1							
	Lamb1-1	laminin B1 subunit 1		10	D	S,R,L	*LAMB1*	7q22 or 7q31	39,40,101,129,144

Continued on next page

Table 1. *Continued.*

New	Locus	Gene name	A	M (cM)	T	Method	H. symbol	H. location	Reference
	lgl	legless		63	D,V	L			97,98,150
	Lm-1	lymphomyeloid antigen-1		44	B	L			121
	Ltrm-1	LTR mink cell focus-forming murine leukemia viral locus-1		25	D	R,L			37,50
	Ltw-2	liver 20-30 thousand M.Wt. protein-3 (provisional)		13	B	R			38
*	*Ly-16*	lymphocyte antigen-16		73	B	L			44
*	*Ly-18*	not used - see Ly-16							
	Ly-18	lymphocyte antigen-18		13	B	R,L			29,108,157
*	*Ly-m18*	not used - see Ly-18							
*	*Lyb-7*	B-lymphocyte antigen-7		45	B	R,L			153
*	*Meta*	meth A tumor antigen		syn	B	S			82,132
	Mmv-6	MCF endogenous virus-6		syn	D	S			68
	Mmv-7	MCF endogenous virus-7		syn	D	S			68
*	*Mmv-18*	MCF endogenous virus-18		--	D	R,L			50
	Mpmv-11	modified polytropic murine leukemia virus-11		30	D	R,L			48,49
	Mpmv-24	modified polytropic murine leukemia virus-24		56	D	R,L			48,49
*	*Mse-1*	esterase modifying locus-1		syn	B	L			30
	Mtv-9	mammary tumor virus locus-9		40	D	S,R,L			13,21,50,64,84,174
	Mtv-30	mammary tumor virus locus-30		2	D	R,L			84
	Mylf-ps	myosin light chain, alkali, fast skeletal muscle, pseudo.		syn	D	S			27
*	*Nmyc*	not used - see Nmyc-1							
	Nmyc-1	neuroblastoma myc-related oncogene-1		4	D	I,S,R	*MYCN*	2p24.1	22,77, 117,143
	Odc	ornithine decarboxylase, structural	1	4	D,B	S,R,L	*ODC1*	2p25	1,10,25,28,91, 134,151,166,170,175
*	*Odc-8*	not used - see Odc-rs8							
	Odc-rs8	ornithine decarboxylase related sequence-8		70	D	R,D			106,137,138
*	*or*	ocular retardation		syn	V	L,C			60
*	*pet*	not used - see hyt							
	Pmv-3	polytropic murine leukemia virus-3		28	D	R,L			47,49,50
	Pmv-27	polytropic murine leukemia virus-27		43	D	R			47
	Pmv-37	polytropic murine leukemia virus-3		3	D	R			47
	Pol-7	viral polymerase-7 (provisional)		4	D	R			139
	Pomc-1	pro-opiomelanocortin-alpha		2	D	S,L	*POMC*	2p23	55,117,126,151,165,100
*	*Pre-1*	not used - see Aat							
*	*Pre-2*	prealbumin-2		49	B,D	L,R	*AACT?*	14q32.1	57,66,67,154,169
*	*Pre-4*	not used - see Pre-2							
	Pygl	liver glycogen phosphorylase		28	D	L	*PYGL*	14q11.2-q24.3	55,113
	Rnr12	ribosomal RNA-12		3	D	R,L,C			3,41,108
	Rnu1a-2	U1a2 small nuclear RNA		20	D	R			92
*	*Rnu3b-rs5*	U3B small nuclear RNA related sequence-5		syn	D	I			96
*	*RP54*	not used - see D12Rp54							
	Rrm2	ribonucleotide reductase M2		syn	D	S,R,L	*RRM2*	2p24-p25	33,162,175
	sm	syndactylism		41	V	L			61,155
	Spi-1	probably Aat							
	Spi-2	probably Pre-2							
	Spnb-1	beta-spectrin-1	1	31	D,B,V	S,R,L	*SPTB*	14q23-q24.2	12,51,81
*	*Synd*	syndecan		3	D	S,L	*SDC*	2	117
	Tgfb-3	transforming growth factor, beta-3		36	D	L	*TGFB3*	14q24	5,35
	Tind	T-peripheral cell antigen		60	B	R,L			125
	Tpo	thyroid peroxidase		syn	D	S	*TPO*	2pter-p12	70,73
	Tpre	pre-T-cell alloantigen		60	B	R,L			122,125
	Tshr	thyroid stimulating hormone receptor		48	D	S,L	*TSHR*	14q31	2,87,104
	Tsu	T-suppressor cell alloantigen		60	B	R,L			123,125
	Tthy	thymocyte alloantigen		60	B	R,L			124,125
	twi	twitcher		29	B,V	L	*GALC*	14q23-qter	155,177
*	*Unit III*	not used - see Mtv-9							
	Xmmv-34	xenotropic-MCF leukemia virus-34		56	D	R			15
	Xmmv-39	xenotropic-MCF leukemia virus-39		56	D	R			48
	Xmmv-50	xenotropic-MCF leukemia virus-50		63	D	R			168

An asterisk in the "New" column denotes a new locus added to last year's list. A "1" in the "A" column denotes an anchor locus. In the "M" column, estimated distances from the centromere are listed in cM. In the "T" column, D = DNA (any locus defined by a DNA sequence or clone); B = biochemical/protein/immunological; and V = visible/other phenotype. In the "Method" column, I = in situ hybridization; S = somatic cell genetics; R = RI strains; L = linkage analysis by backcross or intercross; C = cytogenetic analysis (translocations, visible deletions, etc.); and P = physical mapping (PFGE, YACs, etc.).

Amh-rs4

Typing of NXSM RI strains suggests localization of this DNA sequence to the interval between *Mtv-9* and *Aat* (King et al. 1991).

asp-1, Caa

Young DBA/2 mice are susceptible to audiogenic seizures, while young C57BL/6 mice are resistant, as are (C57BL/6 × DBA/2)F_1 animals and a fraction of F_2

and F_1 × DBA/2 backcross progeny. The observation of a continuous distribution of seizure intensities in these progeny and in BXD RI strains suggested the involvement of multiple genetic loci in determining seizure susceptibility. At the same time, the observation of a strong correlation between inheritance of the DBA/2 allele of *Ah* and susceptibility in the F_2 and backcross progeny, in the BXD RI strains, and in one of two *Ah*-congenic strains, suggested that a locus responsible for a major component of seizure susceptibility, *asp-1,* could be mapped to proximal Chr 12 (Seyfried et al. 1980; Seyfried and Glaser 1981; Palayoor and Seyfried 1984; Neumann and Seyfried 1990; Neumann and Collins 1991).

Localizing *asp-1* on Chr 12 has proven remarkably difficult. The complexities of its analysis are illustrated by comparing the results Palayoor and Seyfried (1984) obtained by typing individuals of each strain (1) with those Neumann and Seyfried (1990) obtained either by typing individuals of each strain (2) or by typing progeny of crosses between individuals of each strain and DBA/2 individuals (3). The strain distribution pattern (SDP) for *Ah* (Cobb et al. 1987; Poland et al. 1987) is shown for comparison. The letters B and D denote C57BL/6J-derived and DBA/2J-derived alleles, respectively. Lower case bold letters highlight the strains showing discordant results between *asp-1* and *Ah* in each SDP.

BXD strain:

	1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 3 3
	1 2 5 6 8 9 1 2 3 4 5 6 8 9 1 3 4 5 7 8 9 0 2
(1)	B D **d** B B D B **b** B B D B B **b** D D D B D **b** B B D
(2)	B D **d** B **d** D **d** **b** B B D B B D D D D B D D B B D
(3)	B D **d** B B D B D **d** **d** D B B D D D D **d** D D B B D
Ah	B D B B B D B D B B D B B D D D D B D D B B D

Considered alone, these data are insufficient to establish linkage at high confidence between *asp-1* and *Ah* or any other mapped marker that has been typed in BXD mice (Neumann 1990; Silver and Buckler 1986). Considered together with the other lines of evidence, these data reinforce the suggestion that complex epistatic interactions determine seizure susceptibility and that available results are insufficient to define and map the individual loci involved.

Palayoor and Seyfried (1984) measured calcium-dependent ATPase activity (*Caa*) in crude brainstem homogenates of BXD mice and observed a continuous distribution of values that correlated positively with the first set of *asp-1* types listed above. This result suggests that a limited number of genes, possibly including some that affect seizure susceptibility, might determine ATPase levels, but do not provide the basis for defining and mapping a gene.

Bcga

Schrier and co-workers (1981) described a phenotype of BCG-induced anergy (assayed as a reduction in footpad swelling), which cosegregated with *Igh-C* in two congenic strains and 23 of 32 backcross progeny. A survey of 23 BXD RI strains (Schrier et al. 1982) defined an SDP consistent with close linkage to *Igh-C* (2 discordancies among 23 strains surveyed), but that also implied the existence of double crossover events in at least two strains not otherwise recombinant in this region of Chr 12:

BXD strain:

Locus	1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 3 3 3 1 2 5 6 8 9 1 2 4 5 6 8 9 0 1 2 3 4 7 8 0 1 2
Aat	B B B D D D D B B D D B D D B B B D D D D B D
	x x x x
Ck-3	B B B D B D D D B D D B B D B B B D D D D D D
	x
Igh-C	B B B D B D D D B D D D B D B B B D D D D D D
	x x
Bcga	D B B D B D D D B D D D B D D B B D D D D D D
	x x x
Igh-V36	B B B D B D D D B D D D B B B B B D B D D D D

The genetic data thus support linkage of *Igh* and *Bcga* and are consistent with the hypothesis that it might be an allele of a *Vh* gene, but do not allow an exact localization of the gene.

bd

Sweet and colleagues (1982) described two sets of backcross progeny in which *bd* was recombinant with *Aat* in 4 of 25 individuals and 18 of 67 individuals, thus placing the gene firmly on distal Chr 12, but not further ordering it.

Caa

See *asp-1*.

Cbg

Leiter (personal communication) has derived an SDP among BXD RI strains for this locus that strongly supports its assignment to distal Chr 12. All placements of *Cbg* imply local double crossover events, so that a precise localization for the marker is difficult:

BXD strain:

Locus	1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 2 3 3 3 1 2 5 6 8 9 1 2 3 4 5 6 8 9 0 1 2 3 4 5 7 8 9 0 1 2
Aat	B B B D D D D B B B D D B D D B B B D D D D B D B D
	x
Spi-2	B B B D D D D B D B D D B D - B B B D D D D B D B D
	x x
Cbg	B B B D D D D B D B D D B B B B B B D D D D B B B D
	x x x x x
Mpmv-24	B B B D B D D D D B D D B B D B B B D D D D B D D D

D12J1

This marker, detected as a PCR product of variable size generated with an arbitrary primer, shows tight linkage to *Igh* in a survey of AXB and BXA RI strains, but cannot be unambiguously ordered (Nadeau et al. 1992).

D12Leh1

This marker, defined by size variation in an interspersed repetitive element PCR product, recombined once with *Pomc-1* and three times with *D12Nyu5* in 48 interspecific backcross progeny, suggesting a location near *Odc* and *Rrm2* on proximal Chr 12 (Cox et al. 1991).

D12Rp54

This gene encodes a liver protein, and a cDNA has been cloned. Variants associated with both the protein and the cDNA have been defined, but no linkage data have been reported (Hill et al. 1982).

Eif4e

Results of typing BXD RI strains indicate tight linkage to *D12Nyu1* (Dorfman et al. 1991), but do not allow the two loci to be ordered:

BXD strain:

Locus	1	2	5	6	8	9	11	12	13	14	15	16	18	19	20	21	23	24	25	27	28	29	30	31	32
Ah	B	D	B	B	B	D	B	D	B	B	D	B	B	D	D	D	D	D	D	B	D	D	B	B	D
		x		x			x	x			x			x		x			x		x			
Eif4e	B	B	B	B	D	D	B	B	D	B	D	B	D	D	D	B	D	D	D	D	D	D	B	D	D
	x																								
D12-Nyu1	D	B	B	B	D	D	B	B	D	B	D	B	D	D	–	–	D	D	D	D	D	D	B	D	D
		x			x		x	x							x	x			x						
Mtv-9	B	B	B	B	D	B	B	D	B	B	D	B	D	D	D	B	B	D	B	D	D	D	B	B	D

Etc-1

This locus specifies an I-E tolerogenic ligand whose expression is correlated with the clonal deletion of certain classes of T cells. It is genetically indistinguishable from the *Mtv-9* proviral locus in 37 RI strains and 48 backcross progeny, and functionally resembles *Mtv-9* in its expression in various tissues and inducibility by mitogens. While not definitive proof that *Etc-1* and *Mtv-9* are synonyms, these data suggest it is appropriate to merge the two loci for the purpose of cataloguing the genetic markers of Chr 12 (Woodland et al. 1991).

Fcr, H-40, Lm-1, Tsu

Fcr specifies a cell surface receptor for the Fc portion of *IgG* found on B lymphocytes; alleles are distinguished according to their affinities for rat *IgG* in a cell-binding assay (Baum et al. 1985). *H-40* is an *Igh*-linked gene, expressed on cells that also bear surface immunoglobulin; alleles are defined by a cell-mediated cytotoxicity assay (Forman et al. 1984). *Lm-1* is also an *Igh*-linked gene whose alleles are defined by a cytotoxicity assay. It differs from *H-40* in being found on T as well as B cells and in the distribution of its allelic forms over inbred strains of mice (O'Toole et al. 1984). *Tsu* is the genetically most extensively studied of the group of serologically defined T cell differentiation antigens that includes *Tind, Tpre,* and *Tthy* (Owen and Riblet 1984).

Tsu has been typed in AKXL RI mice, where it shows 16/17 concordant segregation with *Igh* (Owen et al. 1981), and *Fcr* segregated concordantly with *Igh* in 53 of 78 backcross progeny (Baum et al. 1985). The data that most strongly support the assignment of all four loci to distal Chr 12 and that suggest an order for the loci, however, derive from the analysis of the panel of *Igh*-recombinant strains developed by Riblet and colleagues. These are inbred strains derived from crosses among inbred progenitors and selected for recombination events between *Aat* and the telomere of Chr 12. Assuming each strain to have fixed a single crossover event in this interval in the course of its construction, typing data from the strains best fit the map cen–*Fcr–Lm-1–Aat–Tsu–Igh*. *H-40* appears to fall toward the proximal end of this map but cannot be more precisely ordered (Baum et al. 1985; Forman et al. 1984; O'Toole et al. 1984; Owen et al. 1981). Because the strains arose through a variety of breeding schemes, typing data cannot readily be used to estimate distances among loci.

A variety of lines of evidence suggest that transcriptionally active proviruses can specify cell surface antigens, and several proviruses have been mapped to distal Chr 12. The relationship between the proviruses and markers such as *Tsu, Lm-1, H-40,* and *Ly-16* (below) remains untested, however, because the transcriptional activity of these proviruses is unknown, as is their distribution over the Igh-recombinant strains.

H-17, H-34, H-38, Ltw-2

Polymorphisms associated with these loci have been typed only in the original seven CXB RI strains (Rossomando and Meruelo 1986; Elliot 1979). The resulting SDP is identical for all four loci and identical as well to that found for *Odc, Ah,* and *Ly-18* (proximal Chr 12) and *Il-9, Xmv-13, Gas-1,* and *Amh-rs2* (distal Chr 13; Taylor 1989).

The binomial odds of finding seven concordances on seven tries by chance are 0.0078 [although Taylor (1978) points out that this number is misleadingly

small]; the Bayesian odds according to Silver and Buckler (1986) are 0.48; the Bayesian odds according to Blank et al. (1988) are 0.31; and the Bayesian odds according to Neumann are 0.47. Regardless of the status of these theories, at least one of the suggested assignments of each of the four loci to proximal Chr 12 and to distal Chr 13 must be wrong.

H-40

See *Fcr*.

Hsp86-1, Tshr

A three-point cross strongly supports the gene order *Tshr–Hsp86-1–Igh*, with the outer markers separated by approximately 20 cM (Moore et al. 1991). While the progeny have not yet been typed for any other marker of Chr 12, it is unlikely that *Igh* could be as far as 20 cM from the telomeric end of the linkage map, so these data suggest placement of *Tshr* near *Fos* and *Hsp86-1* near *Aat*.

Igh

The C, J, D, and V DNA sequence elements that make up the *Igh* complex have been identified, and their overall organization within the germline form of the complex has been established. The elements lie on the chromosome in the order cen–*Ca–Ce–Cg2a–Cg2b–Cg1–Cg3–Cd–Cm–J–D–V* (Lai et al. 1989; Shimizu et al. 1982; Wirschubsky et al. 1985). There are four J elements (Newell et al. 1980; Sakano et al. 1980), and twelve D elements have been identified (Wood and Tonegawa 1983). DNA hybridization experiments suggest that the number of *V* genes is between 100 (Brodeur and Riblet 1984) and 1000 (Livant et al. 1986), and many *V* genes and *V* gene clusters have been cloned. Comparison of the sequences of these genes has allowed the definition of a total of 12 *V* gene subfamilies to date (Brodeur and Riblet 1984; Brodeur et al. 1984; Hardy et al. 1989; Meek et al. 1990; Pennell et al. 1989; Tutter et al. 1991; Winter et al. 1985).

The map of the *Igh-C* complex derives only from DNA cloning studies, as no recombination events within the complex have been found (Lieberman 1978).

Only a few recombination events have ever been observed in studies of the *Igh-V* complex (Riblet and Brodeur 1986). Detailed maps of it have been derived from deletional analyses of the rearranged chromosomes of myeloma and hybridoma cell lines. Assuming that the rearrangement that generated the functional *Igh-CJDV* gene in each line was a single event, that the event deleted all germline DNA sequences between the chosen *D* and *V* elements, and that no other DNA sequences were altered in the process, an order for *V* elements can be deduced from a catalog of the elements missing from a series of rearranged chromosomes. Although these assumptions are unlikely to be true in all cases, the results of several such studies are in general agreement, suggesting that *V* elements belonging to different families are often interspersed, that most elements of the J558 and 3609 families are at the distal end of the complex (as is the *Odc-rs8* locus), and that most members of the Q52 and 7183 families are at the proximal end (Brodeur et al. 1988; Kleinfield and Weigert 1989; Krawinkel et al. 1989; Meek et al. 1990; Riblet and Brodeur 1986; Richards-Smith et al. 1992).

This DNA-based view of the organization of the *Igh* complex is not entirely consistent with the earlier model based on the analysis of serologically defined Igh variants. In the *Igh-C* region, the differences are slight, but useful. As well as ordering the *C* genes, DNA cloning studies led to the discovery of switch region variants, which have enriched the catalog of *C* region allelic variants (Marcu et al. 1980). In the *Igh-V* region, the differences are more complex. Serological studies defined 13 idiotypic markers, which have been taken provisionally to define one allele each of 13 distinct loci (Green 1979, 1989). The relation between these functionally defined *Igh-V* genes and the *Igh-V* DNA sequence subfamilies is unclear, however. In two cases, J558 and J606, a single DNA sequence subfamily appears to encode several idiotype markers, and one of the idiotypes, *Igh-Ars*, appears to be associated with members of two DNA sequence subfamilies (Brodeur and Riblet 1984). At the same time, no DNA counterpart has been defined for idiotype markers *Igh-Aa1, Aa2, Aa3, Lev, Ns1, Ns2, Ns3, Ns4, Ns5*, and *Src*. Further, the model of simple allelic relationships between *Igh-V* genes found in different strains of mice is undermined by the demonstration of major differences in subfamily size and organization between different laboratory mouse strains (for example, Brodeur and Riblet 1984; Loh et al. 1983).

The issues of the relationship between *V* gene sequence and idiotype, and of the evolutionary pathway that has produced sequence interspersion are fascinating ones, as is that of the relationship of the *V* gene patterns found in laboratory strains of mice and those found in wild populations of the various species of the genus *Mus* (for example, Blankenstein et al. 1987; Jouvin-Marche et al. 1989). Our concern here, however, is with bookkeeping: how large is the complex genetically, and can landmarks be identified corresponding to its ends for purposes of linkage analysis? The DNA sequence encoding α heavy chains is at the proximal end of the complex, and numerous RFLVs have been found associated with it (for example, Marcu et al. 1980; Blank et al. 1988) in addition to serological variants (Lieberman 1978). The distal end of the complex cannot be uniquely marked: although most of the J558 V gene sequence subfamily can be placed there, individual members of the subfamily are widely dispersed

over the complex, so no distal RFLV can be defined. However, the total genetic distance spanned by the complex appears to be less than 2 cM, and the markers *D12N1* (Bauer et al. 1988; Cho et al. 1991), *Igh-V36* (Cho et al. 1991), and *Odc-rs8* (see which, below) all fall towards its distal end. Thus, precise definition of the distal end of the complex will require physical mapping studies, but the imprecision introduced into linkage analysis by the current gaps in our knowledge is negligible.

iv, lgl

Singh and colleagues (1991) show that *lgl* and *iv* correspond to distinct genes (i.e., distinct transcription units). Half of *lgl/+* progeny from crosses of *lgl/+* and *iv/iv* individuals show situs inversus, but none show the other phenotypes (forebrain, cranial, and skeletal defects) associated with the *lgl/lgl* genotype. Thus, the transgene integration event that caused the *lgl* mutation (McNeish et al. 1988, 1990) and that has been used to define a DNA marker for the locus appears to have disrupted two genes which cannot be resolved by recombination but which can be resolved by the differential results of the complementation test and, perhaps, at a molecular (cDNA) level as well. Inheritance of the DNA marker has been scored in 162 interspecific backcross progeny also typed for *Igh*, and no recombinants were found, confirming the tight linkage of these loci.

Lm-1

See *Fcr*.

Ltw-2

See *H-17*.

Ly-16

Alleles of this gene, a T-cell differentiation antigen, segregate concordantly with *Igh* in 12 inbred and *Igh*-congenic strains, suggesting localization of *Ly-16* to distal Chr 12 (Finnegan and Owen 1981). These data, however, appear not to provide a basis for more precisely localizing the gene.

Lyb-7

Backcross and RI typing data (Subbarao et al. 1979) provide strong support for the assignment of this gene to Chr 12 distal to *Mtv-9*, but the multiple recombination events observed between it and all other markers of this region of the chromosome make further ordering uncertain.

Mmv-18

This proviral integration site shows tight linkage to *Odc* in a survey of NXSM RI mice, and loose linkage to *D12Nyu3* in a backcross (7 recombinants among 43 progeny), placing it on proximal Chr 12 but not precisely localizing it (Frankel et al. 1992).

Mse-1

von Deimling and co-workers (1991) suggest the existence of a gene that modifies the expression of esterase-29, "very closely linked to *Pre-2*" in a backcross, but show no data.

Odc, Odc-rs8

Two genomic DNA sequences strongly reactive with *Odc* cDNA probes have been identified on Chr 12, at the two ends of the linkage map. Data from functional and genetic studies indicate that the proximal locus is the *Odc* structural gene (Table 1). The distal locus, *Ods-rs8*, appears to be a pseudogene. A large number of RI strains have been typed for an RFLV associated with the locus; the resulting SDPs are identical to those of markers of the distal portion of the *Igh-V* complex (0 recombinants among 94 strains with *Igh-V36;* 3 recombinants among 117 strains with *Igh-C;* Richards-Smith and Elliott 1992; Nadeau et al. 1992). Typing of the same *Igh* deletion cell lines used to order *V* gene subfamilies (see *Igh*, above) indicates that *Odc-rs8* lies at or near the distal end of the complex (Richards-Smith et al. 1992).

Pre-2

See *Aat*.

sm, twi

Hawes and colleagues (1980) found 3 recombinants between *Aat* and *sm* among 30 progeny chromosomes examined, and Sweet (1986) found tight linkage between *sm* and *twi*. The markers can thus be assigned to the distal half of Chr 12 with confidence, but not localized further.

Synd

In a survey of 191 interspecific backcross progeny, one recombinant was found between *Pomc-1* and

Synd, three between *Synd* and *Nmyc-1,* and 13 between *Nmyc-1* and *D12Nyu2*. The gene order, *Pomc-1–Synd–Nmyc-1–D12Nyu2,* would require no double crossover events over the interval (Oettinger et al. 1991).

Tshr

See *Hsp86-1.*

Tsu

See *Fcr.*

twi

See *sm.*

Xmmv-39

The status of this locus is unclear. No typing data for it have been published, and the GBASE annotator suggests it to be identical to *Xmmv-34* (Blatt et al. 1983). Frankel and colleagues (1990; W. Frankel, personal communication) distinguish the two loci.

Physical landmarks

Several markers of Chr 12 have been placed in defined regions of the chromosome by in situ hybridization or, in one case, *Meta,* analysis of somatic cell hybrids carrying a chromosome fragment. Physical breakpoints of two chromosomal rearrangements, *T31H* and *In25Rk,* have also been mapped with respect to markers well placed in the linkage map of the chromosome. Figure 1 shows an attempt to assemble a consensus summary of these results. References for specific loci are listed in Table 1.

The breakpoint in Chr 12 of the *T31H* chromosomal translocation falls in band F1; three-point cross results suggested the gene order cen–*Igh–Aat–T31H* breakpoint (Meo et al. 1980; Eicher, E., personal communication). However, karyotypic and molecular analyses of the rearranged copies of Chr 12 found in myeloma cell lines clearly established the location of *Igh* at the breakpoint found in those cells, with *Aat* and *Fos* proximal to it (Ohno et al. 1979; Wirschubsky et al. 1985; Erikson et al. 1986), and linkage analysis of wild-type chromosomes unambiguously establishes the order cen–*Fos–Aat–Igh* (Birkenmeier et al. 1988; Blank et al. 1988). It thus appears to be necessary to postulate that the *T31H* translocation is associated with an additional rearrangement of the affected Chr 12.

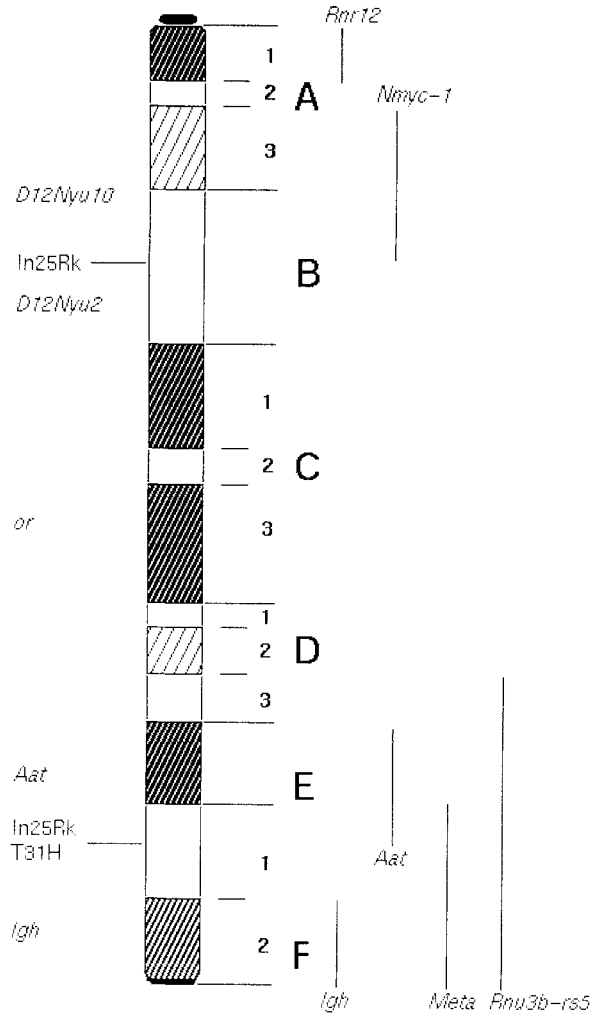

Fig. 1. Localization of markers on the physical map of Chr 12. Gene placements from studies of linkage to rearrangement breakpoints are shown to the left of the idiogram. Those from in situ hybridization and somatic cell genetic analyses are shown to the right.

Typing of *In25Rk* mice for DNA variants suggests that *D12Nyu2* and *Aat* are within the region spanned by the inversion, whereas *D12Nyu10* and *Igh* are outside it (Roderick, T., and D'Eustachio, P. unpublished). If this result is correct, it can be used to refine the physical locations proposed for *Aat* (band E/F; Sifers et al. 1990) and *Nmyc-1* (band A3/B; Klett et al. 1991): *Aat* lies proximal to the *In25* distal breakpoint, hence in band E, while *Nmyc-1* lies proximal to *D12Nyu10,* hence proximal to the *In25* proximal breakpoint (Fig. 1).

The *or* mutation fails to recombine with *In25Rk,* suggesting localization to the region of Chr 12 spanned by the inversion (Hawes and Roderick 1990).

Access to updated report

Send an email request to peter@mcbcm2.med.nyu.edu to receive a current version of this report, including Table 1, as well as updated versions of the tables printed in the first Chr 12 report and not included here.

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