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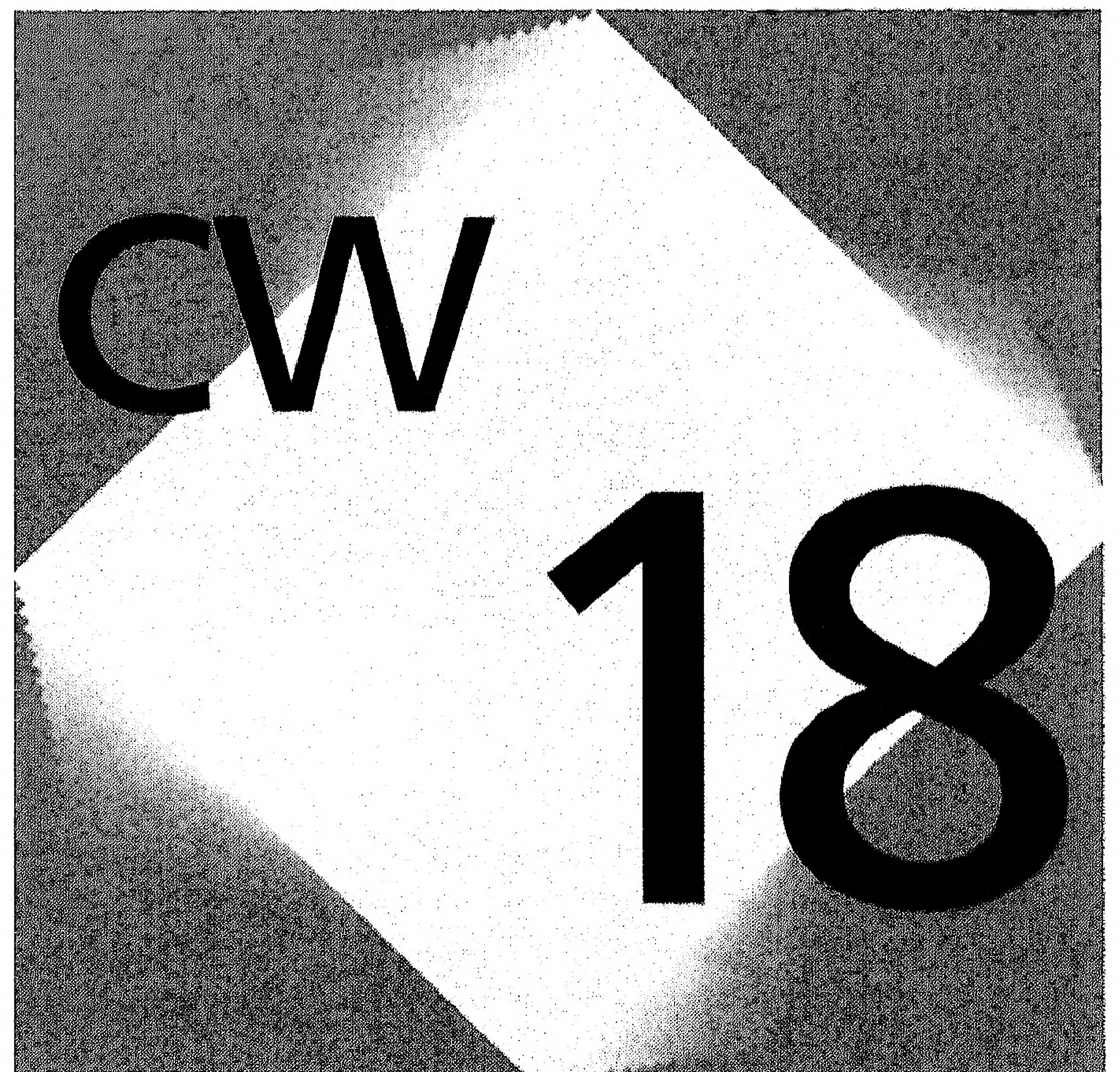
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Report of the
**Fourth International
Workshop on Human
Chromosome 18 Mapping 1996**

held on October 7–9, 1996
Children's Hospital
Boston, Massachusetts

Organized by
Gary A. Silverman
Joan Overhauser
Steve Gerken
Ad Geurts van Kessel



Report of the fourth international workshop on human chromosome 18 mapping 1996

Prepared by: G.A. Silverman, J. Overhauser, S. Gerken, R. Aburomia, P. O'Connell, K.S. Krauter, S.D. Detera-Wadleigh, T. Yoshikawa, A.R. Collins, and A. Geurts van Kessel

The fourth international workshop on human chromosome 18 mapping was held in Boston, Massachusetts, USA on October 7–9, 1996, and was hosted by The Children's Hospital and the Harvard Medical School. The workshop was attended by 34 participants from 7 countries (Canada, Germany, Italy, Japan, The Netherlands, United Kingdom, and United States) and was supported by grants from the National Institutes of Health, the US Department of Energy and the Human Genome Organization (HUGO). The goals of the workshop were to 1) generate integrated genetic and physical maps, 2) update the transcriptional map, 3) assess the syntenic relationships between human chromosome 18 and the mouse genome, and 4) establish a chromosome 18 web site.

The format of the meeting was similar to that used at previous workshops. Abstracts and data from each participant were collected, duplicated and distributed to other participants. Data presentations were organized into five sessions: regional and chromosomal genetic mapping; comparative mapping, regional and chromosomal physical mapping, transcriptional mapping, and databases/world-wide-web (WWW) site. After the data were presented, the

participants were organized into working groups to address issues raised during the discussions and to prepare consensus maps.

A transcript map, using the Whitehead/MIT map as the backbone, was developed using an inferred order from radiation hybrid, STS content, somatic cell hybrid and genetic maps. At least 42 new genes and 213 ESTs were assigned to chromosome 18. A consensus genetic map was constructed using the Location Data Base (LDB). This map contained >600 loci of which 220 were polymorphic, and included markers from the Génethon, CEPH, CHLC, MIT and Utah data sets. A fully referenced hypertext version of this summary map is available through the LDB web site (Table I). Several STS content maps, somatic cell hybrid maps and regional maps were presented. A consensus physical map containing a total of 298 STSs (71 p-arm, 227 q-arm) with an average spacing of 200 kb was assembled.

Revised and new data on disease-related loci were presented. Based on genetic mapping and disease phenotype, Niemann-Pick type C (NPC) and type D are likely to be allelic variants of the same disease locus. A similar conclusion was reached for benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis (PFIC or Byler disease). The NPC/D and BRIC/PFIC loci mapped to the pericentric region (between D18S869 and D18S1101/1108) and 18q21 (between D18S41 and D18S64), respectively. Evidence of linkage disequilibrium between several chromosome 18 loci and two neuropsychiatric disorders (bipolar affective illness and schizophrenia) was provided by several groups.

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Table I. Chromosome 18 WWW sites

WWW Site	URL
Chromosome 18 Home Page	http://www.childrenshospital.org/chromosome18/
The Genetic Location Database (LDB)	http://cedar.genetics.soton.ac.uk/public_html/index.html
UniGene	http://www.ncbi.nlm.nih.gov/Schuler/UniGene/index.html
Stanford Genomic Resources	http://genome-www.stanford.edu/
OMIM Gene MAP-Chromosome 18	http://gdbwww.gdb.org/omim/genemap/docs/18.html
CEPH-G�n�thon integrated map	http://www.cephb.fr/ceph-genethon-map.html
The I.M.A.G.E. Consortium	http://www-bio.llnl.gov/bbrp/image/image.html
Genome Data Base (GDB) Home Page	http://gdbwww.gdb.org/gdb/docs/gdbhome.html
Welcome to G�N�THON	http://www.genethon.fr/genethon_en.html
Welcome to NCBI	http://www.ncbi.nlm.nih.gov
The Cooperative Human Linkage Center	http://www.chlc.org/HomePage.html
Whitehead Institute/MIT Center for Genome Research	http://www-genome.wi.mit.edu/
Human/Mouse Homology Relationships	http://www3.ncbi.nlm.nih.gov/Homology/
MGD: The Mouse Genome Database	http://www.informatics.jax.org/mgd.html
Search the Human Chromosome Set	http://wipux2.wifo.uni-mannheim.de/~son00781/c/omega/topchro2.htm
Chromosome/Homology Search	http://www.hgmp.mrc.ac.uk/DHMHD/chromosome.html
Cross-referencing the Genetics of Model Organisms with Mammalian Phenotypes	http://www.ncbi.nlm.nih.gov/XREFdb/
Links to other Genome Centers	http://mars.uthscsa.edu/Links/genome.html
Genome Databases Menu	http://www.hgmp.mrc.ac.uk/Public/genome-db.html
<i>Caenorhabditis elegans</i> Genome Data	http://eatworms.swmed.edu/genome.shtml
Invertebrate Genome Databases	http://phaedra.crbm.cnrs-mop.fr/Invertebrate-Genome-DBS.html
Integrated Human Gene Map	http://www.ncbi.nlm.nih.gov/SCIENCE96/

A syntenic relationship between human chromosome 18 and the proximal and distal portions of mouse chromosome 18 was supported further by the identification of five new genes. Mouse mutants that may have relevance to human diseases on chromosome 18 also were presented.

The data, maps and abstracts from this workshop can be accessed by the WWW using the Genome Data Base or the Chromosome 18 Home page (Table I).

The genetic map

Large-scale efforts at developing simple-tandem repeat polymorphic loci (STRP) for all human chromosomes and genotyping the CEPH reference families with these genetic markers has occurred at G n thon and the Cooperative Human Linkage Center (CHLC). G n thon published a comprehensive genetic map of the human genome based on 5,264 STRPs (Dib et al., 1996). The genetic map of chromosome 18 spanned 124 cM (sex-averaged) and contained 136 loci with 1.10 markers per cM. The CHLC group published the assignment of 2,931 STRPs to chromosomes using the NIGMS somatic cell hybrid mapping panel 2 (Sunden et al., 1996). A collection of tri- and tetranucleotide STRP markers was used to construct genome-wide human linkage maps using genotypic data collected with the CEPH reference families (Sheffield et al., 1995).

Additional information about the resources developed by these groups can be accessed through the WWW (Table I). Nine genetic maps of chromosome 18 were presented at the workshop. One linkage map spanning chromosome 18 was constructed with CEPH genotypic data using an integrated set of 120 genetic markers from the Utah, CHLC, and G n thon data sets (Table II). Five genetic linkage maps were constructed with genotypes collected in families segregating bipolar disorder and a regional map of 18p11.2→q12.1 was constructed with genotypes from families with bipolar and schizophrenia disorders (Table II). A linkage map flanking the Niemann-Pick type D locus in the pericentromeric region of chromosome 18 was presented. A genetic map based upon meiotic recombination breakpoints in families with familial cholestasis (PFIC/BRIC) was presented for the 18q21→q22 region.

The summary genetic map for the workshop was the integrated physical and genetic map presented by Andrew Collins. The consensus map was comprised of 612 loci, of which 220 were STRPs. The consensus map was updated with the genetic data that were presented at the workshop. The marker orders and genetic distances were incorporated into the LDB and a new integrated map of chromosome 18 was constructed with the LDB software (ldB+/MAP+ suite of programs) (Collins et al., 1996). The updated fully referenced, hypertext version of the consensus map can be viewed on the WWW (LDB, Table I). Comparison of the

Table II. Chromosome 18 workshop summary of genetic maps

Reference	Collins et al.	Gerken et al.	Stine et al.	Berrettini et al.	Rohleder et al.	Gerhard et al.	Wildenaur et al.	Greer et al.	Bull et al.
Map position	18pter-qter	18pter-qter	18pter-qter	18pter-qter	18pter-qter	18pter-qter	18p11.2-q12.1	pericentric	18q21-q22
Number of Loci	220	120	31	28	13	20	16	12	23
Sex average length	128	142	141.5	147	121.15	146	49.5	15	
Male length	107		136		95	119			
Female length	149		157.5		145.3	184			
Map algorithm	likelihood	breakpoints	likelihood	likelihood		likelihood	likelihood	breakpoints	breakpoints
Map program	map+	esort	crimap	crimap		crimap	linkmap		
Pedigrees	CEPH and lod source DB	CEPH	North-American	North-American	German	Amish and Midwestern-American	German and Jewish-Sephardic	Acadian Nova Scotia	Amish and Dutch and Finnish and Costa Rican
Phenotype ^a			BP	Bipolar	Bipolar	BP	BP and Schiz.	NPD	BRIC and PFIC
Number of individuals typed			243	400	377	247	383	152	~350

^a BP: Bipolar affective disorder; Schiz.: Schizophrenia; BRIC: Benign, recurrent intrahepatic cholestasis; NPD: Niemann-Pick Type D

genetic maps with the consensus map for conservation of marker order showed some ambiguities in marker order between the maps.

The coverage of the genetic map is complete for the telomeric regions. sAVA5, a microsatellite repeat containing clone derived from a YAC clone containing an 18pter telomere, was reported to show no meiotic recombination with D18S59 (Vocero-Akbani et al., 1996). The 18qter telomere associated marker, D18S497, was shown by DNA sequence analysis to be identical to the D18S70 locus (Geurts van Kessel et al., 1994). Three gaps of approximately 8 cM (sex-averaged) were observed between D18S52 and D18S464.

Several studies reported a significant difference between the lengths of male and female maps, with the female maps extending an additional 20–60 cM in length compared with the male map lengths (Table II). The decrease in male recombination on 18q was observed, starting near the centromere, in several affected populations and the CEPH reference families.

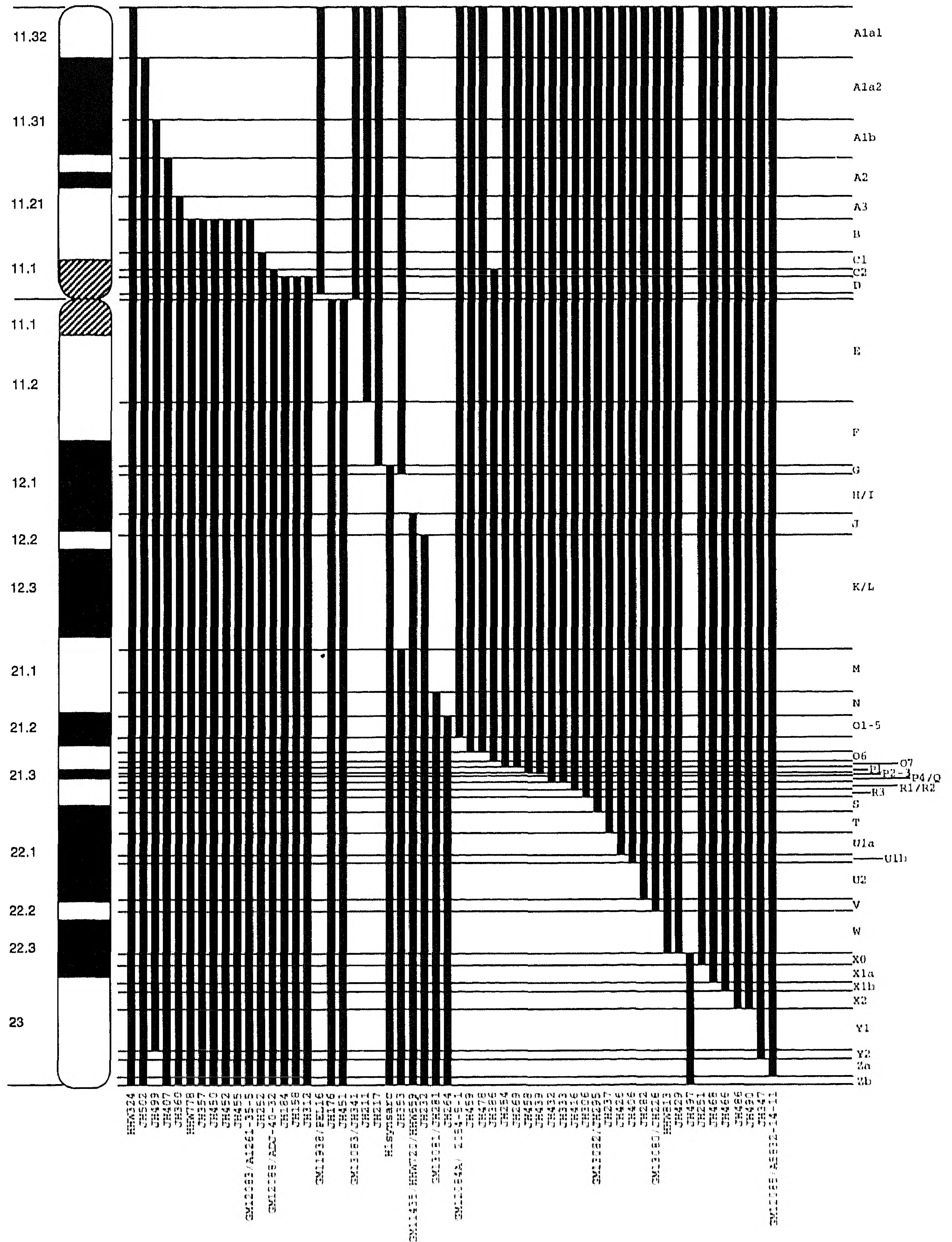
DNA sequence analysis showed that two pairs of STRPs detected the same microsatellite repeat. The DNA sequences of D18S73 and D18S37 were identical. D18S53 and D18S542 have different DNA sequences reported outside of the STS primers. The STRP amplified by both STSs appears to be identical. Recombination between these loci should be reviewed for possible errors in the genotypic data.

The physical map

The resolution of the physical map of chromosome 18 has been improved since the last chromosome workshop (Overhauser et al., 1995). A higher resolution somatic cell hybrid mapping panel was presented by Joan Overhauser. The mapping panel is a composite panel composed of cell lines described previously by Markie et al. (1992) and Rojas et al. (1995), and newly derived cell lines. In addition, a somatic cell hybrid containing the der(X) from a synovial sarcoma cell line that was described by Gilgenkranz et al. (1990) was included. This composite mapping panel is comprised of 56 cell lines and with currently mapped markers, divides the chromosome into 42 distinct bins (Fig. 1).

A chromosome 18 STS content YAC map was presented by Ken Krauter using the Quickmap-based Pooling Strategy (QPS). This YAC map includes over 300 STSs. Chad Nusbaum presented an update on the Whitehead Institute/MIT Genome Center's STS-based map of human chromosome 18. A total of 511 individual markers have been placed on an integrated physical, genetic and radiation hybrid map. The WI/MIT maps contain 324, 1356 and 278 STSs respectively. The marker set also contains 261 ESTs. Current efforts are focused on map verification, transcript (EST)

Fig. 1. Somatic cell hybrid mapping panel. An ideogram of chromosome 18 is shown to the left. The black bars represent the amount of chromosome 18 material present in each cell line. The bin names are shown at the right. If the cell line is available at the NIGMS Human Genetic Mutant Cell Repository, its catalogue name is included.



mapping and cytogenetic integration by FISH mapping with STS-containing BACs. Several region-specific YAC contigs were presented and included the 18p11 region (Lisa Esterling), the Niemann-Pick Disease type D locus within 18q11 (Wenda Greer and Christie Riddell), the desmocollin locus within 18q12.2 (Joachim Arnemann), the BRIC/PFIC locus within 18q21.1 (Nelson Freimer), and the 18q- critical region within 18q23 (Joan Overhauser).

A consensus ordered STS content map for chromosome 18 was generated (Fig. 2). The STS content map generated by

Ken Krauter served as a framework for map construction. Additional markers were added where order could be inferred using data presented by others. An STS content YAC contig of 18p was recently published by Giacalone et al. (1996) and this information was incorporated into the map. If order for large regions could not be determined, due to the use of different markers within a region, the additional STS order information was included on the left side of the consensus map (Fig. 2). If differences in STS order could not be resolved, the alternative order of markers was placed at the

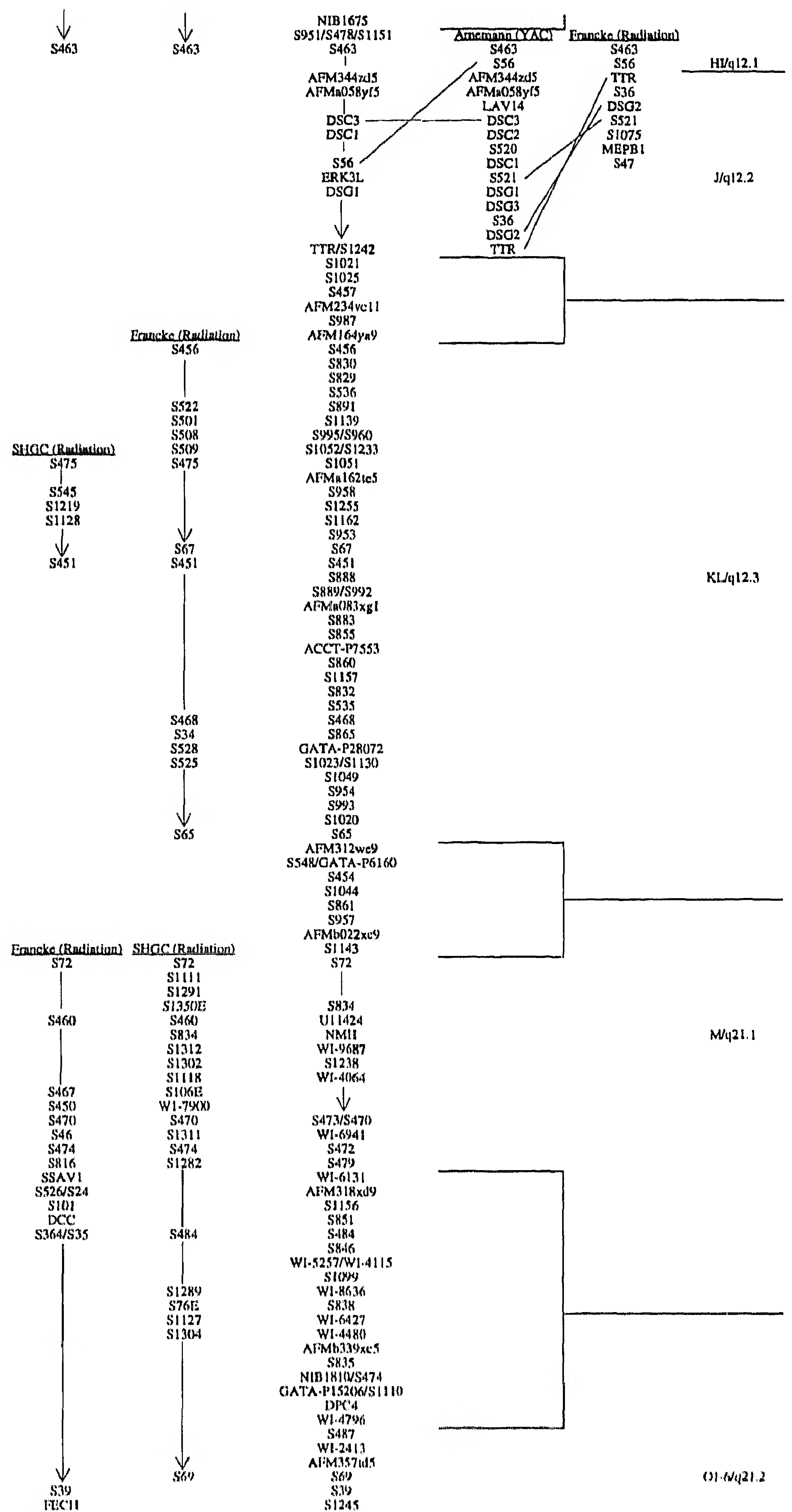


Fig. 2. continued

chromosome 18. Sevilla Detera-Wadleigh reported on the current status of the chromosome 18 transcript map. A concerted effort to sequence cDNAs and to generate ESTs by several groups, notably the Washington University/Merck collaboration, has resulted in a large number of novel, ready-to-map sequences. In addition, the development of radiation hybrid (RH) mapping panels at the Stanford Human Genome

Center (SHGC) and their availability through Research Genetics, has permitted rapid and high resolution mapping of ESTs. The genome project at the Whitehead Institute/MIT has generated an RH map that included a total of 139 ESTs and genes. The SHGC RH map contained 26 ordered cDNAs and 54 unordered cDNAs localized to 40 bins. The National

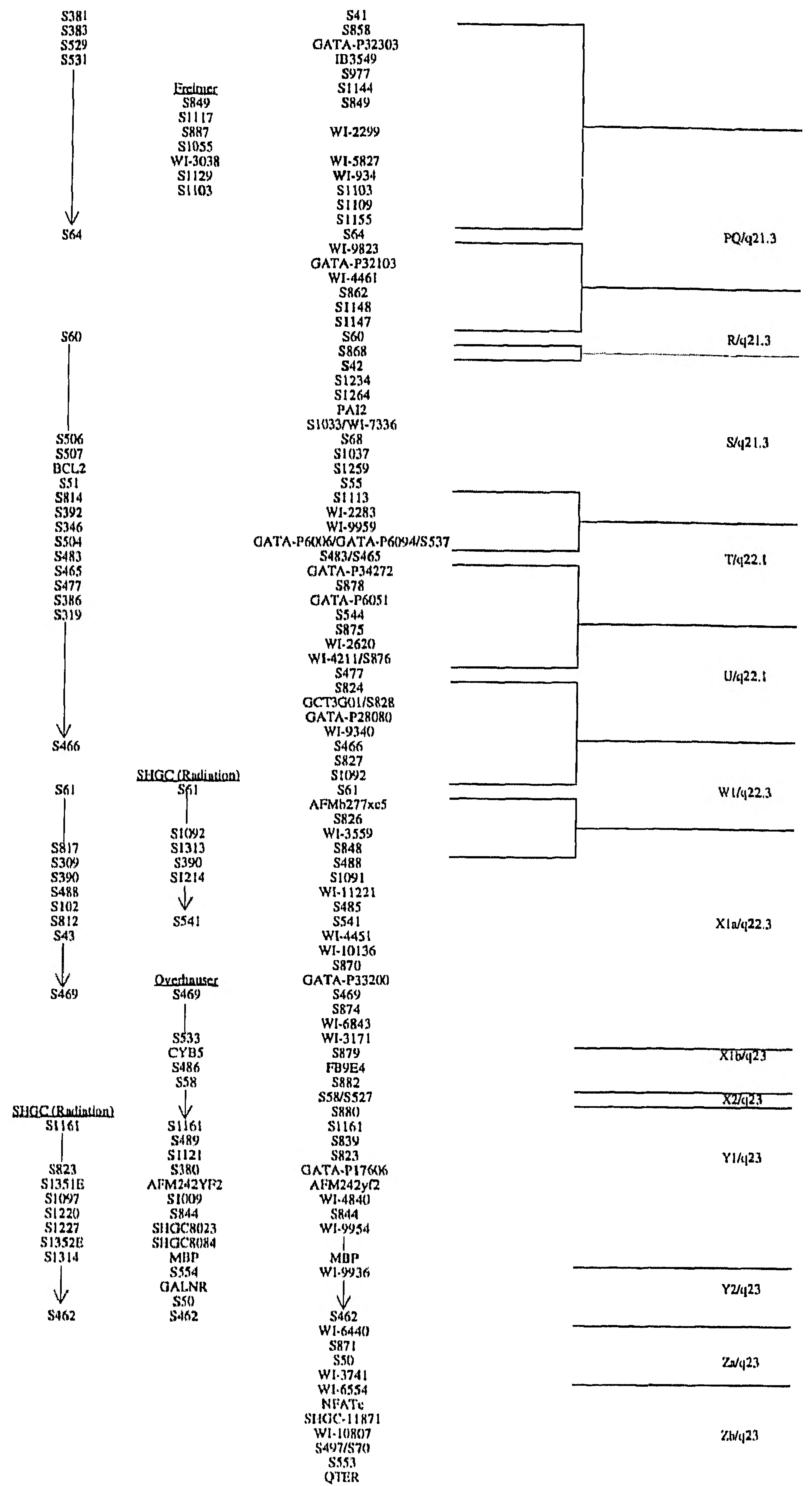


Fig. 2. continued

Center for Biotechnology Information (NCBI) Entrez map added another 12 cDNAs. Sevilla Detera-Wadleigh reported on the isolation of 25 novel transcripts and their mapping using the chromosome 18 hybrid panel (Joan Overhauser) and the SHGC G3 RH panel. The SYT, desmocollin (DSC), and desmoglein (DSG) genes were integrated into the transcript map. Takashi Imamura reported on the generation of 55 different transcripts by cDNA selection using chromosome 18 cosmids. Nine of these transcripts were novel. Using the WI/MIT transcript map as a backbone, an integrated consensus transcript map was assembled (Fig. 3). Repetitious transcripts were ordered into groups and localizations were improved and inferred when possible.

Fig. 3. Transcript map of chromosome 18. The Whitehead Institute/MIT RII map of ESTs was used as the backbone of the map. WI SHGC, and NCBI ESTs are indicated. ESTs reported by Yoshikawa at this meeting are preceded by a clone number. Known genes are indicated by their gene symbol in bold type. ESTs with homology to other genes are depicted in bold type in parentheses. Asterisks indicate UniGene EST clusters with the first member's GenBank number indicated after the asterisk. Dashed lines refer to additions to the WI/MIT map. Vertical bars represent approximate physical locations.

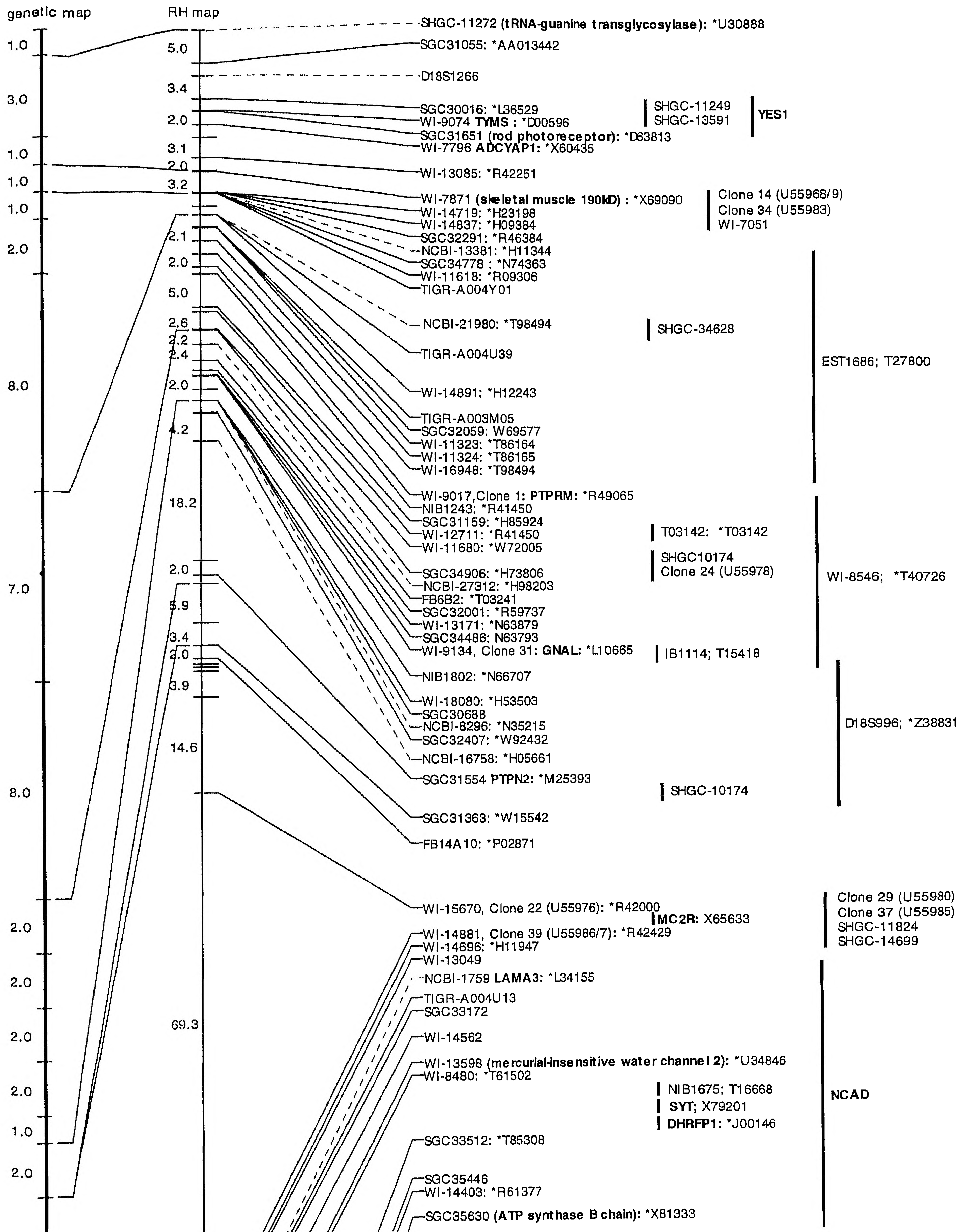


Fig. 3.

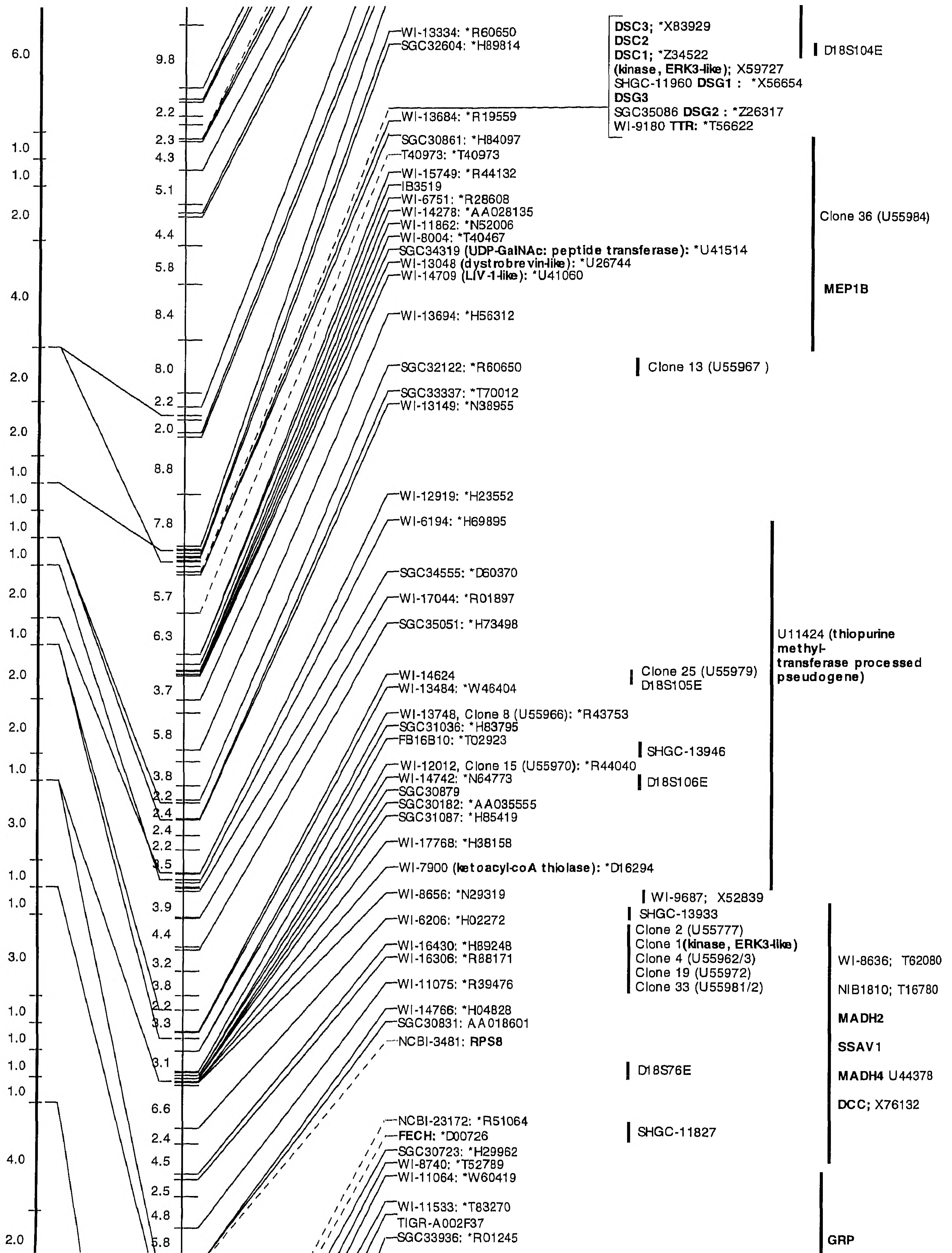


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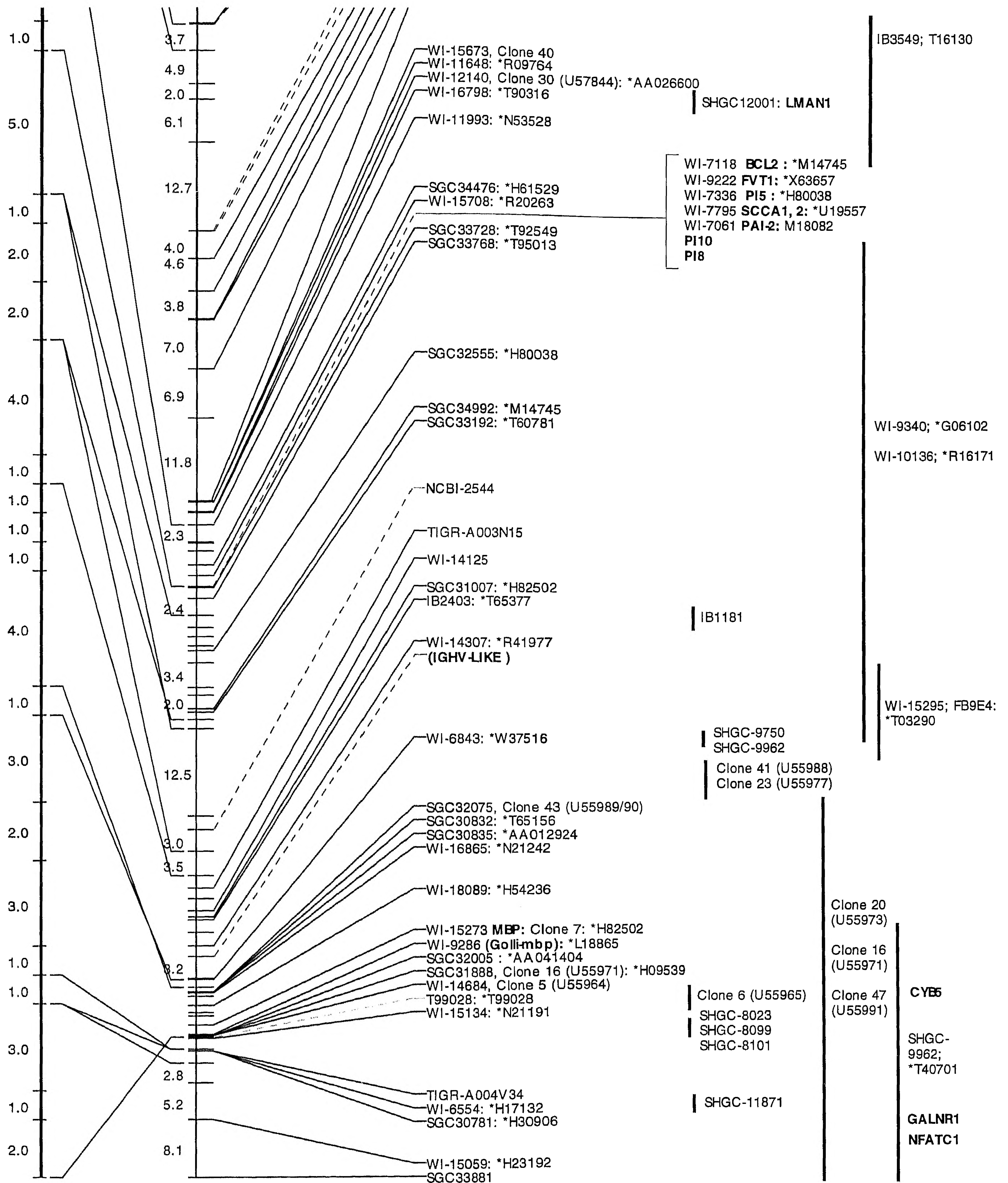


Fig. 3. continued

Table III. Syntenic relationships between human chromosome 18 and the mouse genome

Human chromosome	Human gene	Mouse chromosome	Mouse gene	Mouse locus
18p11.2	MC2R	18	<i>Mc2r</i>	37.0
18p11	GNAL	18	<i>Gnal</i>	41.0
18p11	PTPN2	18	<i>Ptpn2</i>	syntenic
18p11.2	PTPRM	17	<i>Ptpm</i>	38.0
18p11.2-p11.3	LAMA	17	<i>Lama1</i>	38.0
18q11	NICA	18	<i>Nica</i>	syntenic
18q11			<i>ataxia</i>	3.0
	LAMA3	18	<i>Lama3</i>	4.0
	Tg-9257	18	<i>Tg9257</i>	4.0
18q12.1			<i>Evi3</i>	5.0
			<i>Catn1</i>	5.0
	CDH2	18	<i>Cdh2</i>	6.0
			<i>Pou4f3</i>	6.0
18q12.1-q12.2	TTR	18	<i>Ttr</i>	7.0
	DSG1		<i>Dsg1</i>	7.0
	DSG3		<i>Dsg3</i>	7.0
	DSC3		<i>Dsc3</i>	7.0
			<i>balding</i>	7.0
18q12	MEP1B	18	<i>Mep1b</i>	8.0
			<i>Lanceolate</i>	8.0
			<i>hair</i>	
18q12	NPC, NPD	18	<i>spm</i>	11.0
18q21	EST00250	18	<i>D18xrf118</i>	syntenic
18q21.1-q21.31	FECH	18	<i>Fech</i>	39.0
18q21.32-q21.33	GRP	18	<i>Grp</i>	40.0
18q21.1	DCC	18	<i>Dcc</i>	45.0
			<i>cmo</i>	45.0
18q21.3	BCL2	1	<i>Bcl2</i>	59.8
18q22.1	PAI2	1	<i>Planh2</i>	61.1
18q23	MBP	18	<i>Mbp (shi)</i>	55.0
	GALNR	18	<i>Galnr</i>	55.0
	WI-15059	18	<i>Spalt</i>	55.0
	PEPA	18	<i>Pep1</i>	syntenic
18q23	CBLN2	18	<i>Cbln2</i>	58.0
	NFATC	18	<i>Nfatc</i>	syntenic

Comparative Mapping

The relationships between human chromosome 18 and the mouse genome were discussed by Denise Simoneaux and Andrew Griffith. Most genes that map to human chromosome 18 map to the proximal and distal ends of mouse chromosome 18. Exceptions include a block at human 18p11 (LAMA, PTPRM) that maps to mouse chromosome 17, and a block at 18q21→q22 (BCL2 and PAI2) that maps to mouse chromosome 1 (Table III). The human-mouse gene order is similar, with the exception that genes mapping to distal human 18p (MC2R, GNAL) appear to reside in the portion of the mouse map corresponding to human 18q21.

New genes that map to both species are EST002: (Brugia malayi filarial antigen homologue), the galan receptor (GALNR1), *spalt* (homologous to a Drosophila homeotic transcription factor), cerebellin 2 (CBLN2) and the NFATC transcription factor. A transgene insertion (Tg-9257) on mouse chromosome 18 resulted in craniofacial and inner ear malformations (Griffith et al., 1996a). Tg-9257 was reported to have a homologous DNA segment on human 18 (Griffith et al., 1996b). Other mouse mutants with potential human homologues are ataxia (*ax*) and *twirler* (inner ear and craniofacial malformations, obesity). Many interesting mouse mutants were discussed as possible models for diseases of human 18. These include sphingomyelinosis (*spm*, a possible model for NPC/NPD), balding (*bal*; hair loss, immunologic defects), lanceolate (*lah*; hair breakage and alopecia, possible model for Netherton Syndrome), and chronic multifocal osteomyelitis (*cmo*; bone inflammation and possible model for familial expansile osteomyelitis). The mouse ortholog of SYT (*Syt*) was cloned recently and found by FISH, to map to mouse chromosome 18, region B1 (de Bruijn et al., 1996). Further information regarding mouse human homologies cited herein can be obtained from the Mouse Chromosome Committees, whose reports can be found at the Mouse Genome Database (Table I), and in a report assembled by DeBry and Seldin (1996) (see WWW Human/Mouse Homology, Table I).

In two separate studies, genes from human chromosome 18 were found to be syntenic with bovine chromosome 24. Larsen et al. (1996) used PCR and a panel of bovine/rodent hybrid cell lines to map the bovine orthologs of TYMS, ADCYAP1, MC2R, TTR, CDH2, GRP and PAI2 to bovine chromosome 24. Solinas-Toldo et al. (1995) used FISH to map the bovine desmocollin genes, DSC1-3, to 24q21→q22.

Edwin McConkey used FISH to examine the origins of human chromosome 18 from a human/ape ancestor. Using probes from 18p and the pericentric region, he showed that human chromosome 18 may have arisen from a pericentric inversion involving the short arm and elements near the centromere.

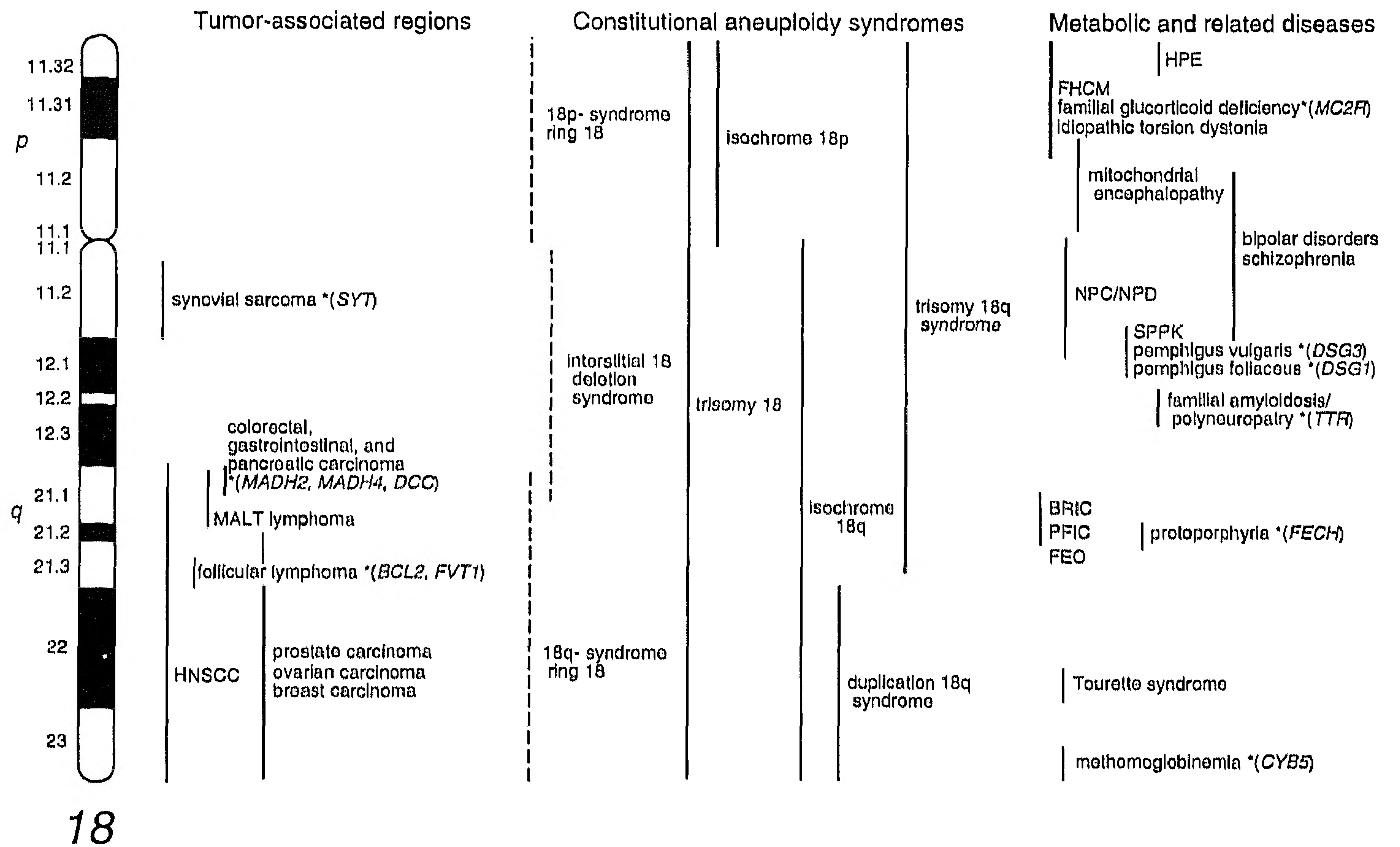
New genes and disease-related studies

A summary map of chromosome 18 diseases was updated and is presented in Fig. 4.

Bipolar disorder

Wade Berrettini, Hendrik Rohleder, Daniela Gerhard, and Colin Stine presented genetic linkage studies in pedigrees with bipolar affective disorders. Three of the four studies reported increased sharing for paternal pedigrees at various loci across chromosome 18. Berrettini reported that a parent-of-origin analysis of his original 22 family sample (Berrettini et al., 1994) confirmed the observations of Stine et al. (1995). The data showed an excess allele sharing for kindreds in

Fig. 4. Diseases associated with chromosome 18. The approximate chromosome location of the disease is indicated by a vertical line. Candidate genes for certain diseases are identified by an asterisk with the gene symbol in parentheses. Regions duplicated or deleted in aneuploidy syndromes are depicted by solid or dotted lines, respectively (Silverman and Overhauser, 1996).



which at least one paternal transmission of illness occurred, but no excess allele sharing in other kindreds. The linkage was observed between D18S62 and D18S66, the pericentromeric region. Rohleder, and colleagues performed parametric lod score analysis and obtained a maximum 2-point lod score of 1.91 ($\theta = 0.0$) in paternal pedigrees and no evidence of linkage in maternal pedigrees. Gerhard et al. did not find positive findings in the 2 large pedigrees (the Old Order Amish and midwestern American) using parametric and non-parametric methods and markers spanning the entire chromosome. Stine et al. reported a re-analysis of their paternal pedigree data (Stine et al., 1995) using a two-locus model. The best lod score (4.9) was generated for an epistatic two-locus model that requires a locus on 18p with a recessive mode of inheritance and an allele on 18q with dominant inheritance. Detera-Wadleigh et al. reported the results of linkage disequilibrium analysis of chromosome 18 on two family samples: 1) the 22-family sample of Berrettini et al. (1994) and 2) 97 families collected through the NIMH Genetics Initiative. While no evidence of linkage was detected in the Genetics Initiative families by the affected sib pair method, evidence of linkage disequilibrium was detected at D18S53, D18S1116, and D18S115 in the Berrettini sample. In addition, a new transcript isolated by Yoshikawa et al. and associated with biallelic polymorphism on 18p showed linkage disequilibrium between allele 2 and the bipolar phenotype in both family samples. Supporting the earlier report by Freimer et al. (1996), linkage disequilibrium was also detected at D18S469 in the Genetics Initiative sample.

Deleted in colorectal carcinoma (DCC) gene

Diffusible chemoattractants and chemorepellents play an important role in establishing correct neuronal connections. One family of these molecules, the netrins, is conserved in vertebrates, *C. elegans* and *D. melanogaster*. Recently, DCC and its homologs in *C. elegans* (*unc-40*) and *Drosophila* (*frazzled*) were shown to be transmembrane protein receptors that bind members of the netrin family (Keino-Masu et al., 1996; Kolodziej et al., 1996; S.-Y. Chan et al., 1996).

Familial cholestasis

The map location for two forms of autosomal recessive familial cholestasis has been refined since the previous workshop (Carlton et al., 1995). Nelson Freimer presented results from haplotype and recombination evaluation of over 70 pedigrees for Benign Recurrent Intrahepatic Cholestasis (BRIC) and Progressive Familial Intrahepatic Cholestasis (PFIC or Byler disease). These pedigrees were collected in collaboration with Roderick Houwen, Alex Knisely and Peter Whittington. Both BRIC and PFIC are localized to within a region of ~4 cM between D18S41 and D18S64.

Galanin receptor 1

Galanin is a neuropeptide that stimulates growth hormone secretion and also inhibits vagal tone. The peptide acts via a seven-trans-membrane-spanning, G-protein-coupled receptor. Nicholl et al. (1995) mapped the galanin receptor (*GALNR1*) to 18q23 by FISH.

Idiopathic torsion dystonia (ITD)

ITD is a heterogeneous group of inherited movement disorders. The most common form is inherited in an autosomal dominant fashion with reduced penetrance. Genetic analysis using a pedigree with a high density of dystonia individuals showed linkage to 18p (telomeric to D18S1153) with a maximal lod score of 3.17 (Leube et al., 1996).

Mothers against decapentaplegic-related (MADR) genes: DPC4 and MADR2/JV18

TGF β and related proteins play important roles in regulating cellular proliferation and stimulating differentiation. These proteins interact with serine/threonine kinase, cell-surface receptors. Although not well understood, MADR proteins function downstream in the TGF β signal transduction pathway. Loss of MADR genes in certain tumors may enhance their growth. Hahn et al. (1996) identified an MADR gene, MADH4 (alias DPC4; Smad4 family), that was homozygously deleted in ~30% of pancreatic carcinomas. This gene was located ~0.7 Mb centromeric to DCC, another putative tumor suppressor gene. A second MADR gene, MADH2 (alias MADR2 or JV18-1; Smad2 family) was deleted or mutated in a subset of colorectal tumors (Eppert et al., 1996; Riggins et al., 1996). MADH2 maps to 18q21.1, ~3 Mb centromeric to MADH4.

Niemann-Pick disease type D (NPD)

NPD, like NPC, is a progressive, degenerative disorder that results in the accumulation of cholesterol and sphingomyelin. NPD has been reported only in descendants of an Acadian couple that lived in Nova Scotia. Wenda Greer and Christie Riddell presented data showing that NPD is tightly linked ($\theta = 0.00$; $Z_{max} = 3.62$) to D18S480. The NPD locus is flanked by markers D18S869 and D18S1101. This pericentric region of 18q also appears to be the location for NPC (Carstea et al., 1993), which suggests that the two disorders may be allelic variants of the same gene.

Schizophrenic disorders

Dieter Wildenauer reported sib-pair and lod score analysis in 59 families (383 members, 155 affected) suggesting a susceptibility locus near D18S53 for schizophrenia and schizo-affective disorder, schizophrenic type (Research Diagnostic Criteria). Multipoint sib-pair analysis using a broad definition of the affected phenotype which includes an additional 25 individuals with affective disorder revealed a lod score of 3.2 (all possible pairs) and 2.3 (independent sib pairs). In addition, multi-allelic TDT analysis revealed significant evidence of linkage disequilibrium between a polymorphic allele at the G_{01f} locus and the broad definition of the affected phenotype.

Striated form of palmoplantar keratoderma (SPPK)

Palmoplantar keratoderma is a hereditary disorder of keratinization with several clinically, histopathologically and genetically distinguishable phenotypes. Joachim Arnemann discussed the data by Hennies et al. (1995) who mapped an autosomal dominant striated form of palmoplantar keratoderma (SPPK) with hyperkeratotic bands on palms and soles by linkage analysis to 18q12. The disorder mapped between markers D18S36 and D18S536 with a maximum lod score for D18S536 ($Z_{max} = 3.3$ at $\theta = 0.00$). The disease localizes within or close to the cluster of desmosomal cadherins, as Joachim Arnemann and Roger Buxton mapped D18S36 within the desmoglein cluster at 18q12 (Simrak et al., 1995). Desmosomal cadherins are potential candidates for this disease as they link via desmosomal plaque proteins to the keratin intermediate filament bundles.

Synovial sarcoma

The t(X;18)(p11.2; q11.2) is found in more than 90% of human synovial sarcomas. The occurrence of two related but distinct breakpoints at Xp11.2 has been observed using tumor-derived somatic cell hybrids and FISH in primary tumor samples with breakpoint-spanning YACs. The isolation of chimaeric (X;18) breakpoint fragments and the corresponding genes SYT (chromosome 18) and SSX (X chromosome) were described by Ad Geurts van Kessel. Sequence analysis of RT-PCR products from different synovial sarcomas revealed two alternative fusion products, SYT-SSX1 and SYT-SSX2, that relate to the two alternative breakpoints in Xp11.2. The *SIT* gene is flanked by the markers DHF-P1 and D18S1038.

Transthyretin related hereditary amyloidoses

Several missense mutations in the TTR gene, which maps to 18q12, are associated with transthyretin-related hereditary amyloidosis (TTR-HA). In previous studies, 9 different mutations were detected in the TTR gene in several unrelated Italian families affected by TTR-HA (Ferlini et al., 1992; Ferlini et al., 1994). Laura Obici described a new TTR variant, Arg47, in two unrelated Italian families. The substitution results from two different nucleotide changes (G to A and G to C) at the same position in the penultimate nucleotide of exon 2. The G to A transition represents a novel point mutation. Haplotype studies in 6 Italian families with the Met30 variant demonstrated multiple origins of this mutation in Italy (Almeida et al., 1995). TTR transcription studies were performed in several different human fetal tissues by RT-PCR. The full length transcript was observed in the fetal liver, eyes and brain. A high amount of RNA was found unexpectedly in the cerebellum and low levels were present in the kidney and the spinal cord.

18p- syndrome

Joan Overhauser used somatic cell hybrids established from several patients with the 18p- syndrome, STS mapping,

and FISH to characterize the extent of chromosomal loss in this disorder. One patient with many features of the 18p-phenotype had a 4-Mb terminal deletion of 18p11.2. This critical region contains the genes TYMS, YES1 and ADCYAP1.

18q- syndrome

Peter O'Connell used a chromosome 18 genomic library to perform direct selection of a lymphoblastoid cDNA library. A total of 3000 cDNAs were selected. A subset of 35 chromosome 18 cDNAs were isolated and mapped using a chromosome 18 somatic hybrid panel. Twelve cDNAs mapped to that portion of 18q which is lost in most patients with the 18q- syndrome. Northern blot analysis of lymphoblastoid RNA showed that the steady state levels of one of the transcripts (an EF1 homologue) was increased in 18q- syndrome patients relative to that of normal controls.

At the previous workshop, mapping of a critical region for the 18q- syndrome to the distal portion of the long arm was reported. The critical region has been narrowed further by Joan Overhauser. Molecular analysis of the del(18)s from a mother and daughter, who display the major phenotypic features of 18q- syndrome, revealed a terminal deletion from D18S1121. Recently, several candidate genes for phenotypes of the syndrome map to the region. These include GALNR1 (galanin receptor 1), a neuropeptide which is in the pathway for growth hormone secretion and NFATC, a lymphoid-specific gene which may be involved in IgA deficiency. Takashi Imamura reported 31 ESTs and Sevilla Detera-Wadleigh reported 13 ESTs which map to the 18q- region. This represents a four-fold increase in the number of genes that map to the 18q- critical region.

18q21 serpin locus

Allison Bartuski presented a PCR analysis of YAC clones spanning the 18q21 serpin cluster (Schneider et al., 1995). Two new serpins, cytoplasmic antiproteinase 2 (PI8) and bomapin (PI10) mapped to the cluster. The order of the six serpins was cen-PI5, SCCA2, SCCA1, PAI2, PI10, PI8 -tel.

Chromosome 18 telomeres

Reithman and colleagues isolated telomeric YACs from both the q-arm (yRM2050) and p-arm (yRM2102) of chromosome 18 (Reithman et al., 1989). A microsatellite

marker CU18-010 (D18S497) was isolated from yRM2050 and found to be identical to D18S70 (Geurts van Kessel et al., 1994). Vocero-Akbani et al. (1996) reported on two additional 18q and p clones, TYAC118 and TYAC89 (89.115), respectively. From the latter clone, they isolated a simple sequence repeat, sAVA5 (Genbank U53012) that maps 0 cM from D18S59. Thus, the simple sequence repeat markers sAVA5/D18559 and D18S497/D18S70 delineate the ends of short- and long-arms, respectively, of chromosome 18.

Pseudogenes

Pseudogenes for FAU1 (Finkel-Biskis-Reilly murine sarcoma virus associated ubiquitously expressed) (Kas et al., 1995), cyclophilin A (Willenbrink et al., 1995) and the interleukin 9 (Kermouni et al., 1995) receptor have been mapped to chromosome 18. Only the IL9RP was regionally localized to 18p11.3.

World-Wide-Web Site

A chromosome 18 home page was prepared by Rami Aburomia and now appears on the World-Wide-Web. Reports from past and present (1996) chromosome 18 workshops, as well as abstracts, consensus maps, and hypertext links to other sites of interest appear on this home page (see Table I for the URL). The Web interface gives the user the ability to browse information and quickly cross-reference with other on-line databases.

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The complete abstract can be found in GDB.

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The World Wide Web as a method and source for dissemination of genetic and biological information (CIT:763395)

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An integrated genetic map of human chromosome 18 (CIT:763411)

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The desmosomal cadherin gene cluster at 18q12.1 (CIT:763402)

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Cytoplasmic antiproteinase 2 (PI8) and bomapin (PI10) map to the serpin locus at 18q21.3 (CIT:763400)

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A linkage study of bipolar illness (CIT:763482)

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Refining the location of the BRIC/PFIC gene through identification of shared haplotypes (CIT:763397)

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An integrated map of chromosome 18 (CIT:763396)

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Molecular, genetic and transcriptional analysis in the transthyretin gene (CIT:763410)

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A linkage map of chromosome 18 based on the genotypes from 2 large kindreds segregating affective disorder (CIT:763404)

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The SYT and SSX Genes in t(X;18)-positive human synovial sarcomas (CIT:763401)

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Linkage of Niemann-Pick Disease Type D to chromosome 18q11 (CIT:763398)

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Comparative mapping of human chromosome 18 and mouse chromosome 18 (CIT:763405)

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An integrated physical map of human chromosome 18 (CIT:763399)

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Evolution of human chromosome 18 (CIT:763406)

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An STS-based map of human chromosome 18 (CIT:763412)

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Chromosomal syndromes and somatic cell hybrid mapping (CIT:763407)

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Investigation of a bipolar affective disorder locus on the short arm of chromosome 18 (CIT:763413)

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cDNA selection: Efficient PCR approach for the selection of cDNAs encoded in chromosome 18 DNA fragments (CIT:763480)

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Comparative mapping of human-mouse chromosome 18 (CIT:763408)

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Differential gene expression in lymphoblastoid cells from patients with 18q- syndrome (CIT:763481)

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18p - A susceptibility locus for affective and schizophrenic disorder? (CIT:763409)

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Evidence for the presence of two loci for bipolar affective disorder linked to chromosome 18 (CIT:763414)

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Isolation and physical mapping of chromosome 18 brain-expressed transcripts (CIT:763403)