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Report of the
Third International Workshop on Human Chromosome 18 Mapping 1995

held on May 8–9, 1995
at Thomas Jefferson University
Philadelphia, Pennsylvania, USA

Organized by
Joan Overhauser
Gary A. Silverman
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Report of the third international workshop on human chromosome 18 mapping 1995

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The third international workshop on human chromosome 18 mapping was held in Philadelphia PA, USA on May 8–9, 1995, and was hosted by Thomas Jefferson University. The workshop was attended by 28 participants from 6 countries (United States, The Netherlands, Italy, United Kingdom, Germany, and Japan), and was supported by the National Institutes of Health, Department of Energy, HUGO, and the Netherlands Organization for Scientific Research (NWO). The major goals of the workshop were: 1) to assimilate the latest information on the mapping of disease-related genes on chromosome 18; 2) to prepare consensus genetic and physical maps, both at the regional and chromosomal level; 3) to document resources that are available to the chromosome 18 mapping community; 4) to foster collaborations between investigators that have mapping efforts involving chromosome 18; and 5) to ensure that the Human Genome Data Base is up-to-date through the entry of information derived from data presented at the workshop.

Data from all of the participants were collected at the beginning of the meeting. This information was photocopied and distributed among all participants. Short presentations were made by each participant to provide the most current mapping data and disease gene identifications. Several presentations reported on efforts to physically and genetically map the chromosome. Working groups were formed to prepare consensus genetic and physical maps for each region of the chromosome as well as to integrate these maps wherever possible.

Since the second international workshop on human chromosome 18 mapping, July 19–20, 1993 (Geurts van Kessel et al., 1994), 14 new genes have been assigned to chromosome 18 and include RLCA, RLCB, ERGIC-53, SCCA1, SCCA2, MASPIN, MCR5, NFATC1, NFATC2, DSC1, DSC2, DSC3, SYT, and MEP1B. Refined localizations were obtained for holoprosencephaly, Niemann Pick Type C, ACTH receptor, bipolar disease and familial expansile osteolysis. Several new diseases were mapped to chromosome 18 including familial hypertrophic cardiomyopathy, a second bipolar disease locus, a second Niemann Pick Type C locus, benign recurrent intrahepatic cholestasis, and progressive familial intrahepatic cholestasis.

A total of 5 single locus and 13 multilocus YAC contigs were described, including the markers D18S460, D18S470, D18S484, D18S64, BCL2, D18S466, D18S485, D18S469, D18S380, MBP, and DSG. Two of the contigs partially overlap (D18S64 and MBP). The DSG contig encompasses all DSG (3) and DSC (3) loci as well as TTR. Two overlapping YACs contain four serpin genes. One of the D18S64 contigs spans the familial expansile osteolysis candidate region and one of the MBP contigs spans the 18q–syndrome minimal critical region.

The number of D segments increased to 982 and the number of STSs to 1514.

The genetic map

Various laboratories have been involved in large scale efforts to create high-resolution genetic maps for all of the human chromosomes. Several such maps have been published since the second international workshop (Gyapay et al., 1994; Buetow et al., 1994; Utah, in press). Four genetic linkage maps spanning chromosome 18 were presented at the meeting. As part of a genetic analysis of the association of loci on chromosome 18 with bipolar disorder...
Two panels of radiation-reduced somatic cell hybrids were described by Robin Leach (University of Texas Medical Branch, Galveston, TX) and the rapid construction of high-resolution genetic maps for chromosome 18 was determined to be no longer necessary. This determination was based upon the report that completion of the physical map on chromosome 18 was expected within the next two years and the fact that the majority of the STRP markers are PCR-based, are on the physical map and detect loci with heterozygositys greater than 0.70.

The physical map

The resolution of the physical map of chromosome 18 has been greatly improved by the availability of human YAC libraries and clones to all scientists as well as the concerted efforts to map STSs and genes to a set of somatic cell hybrids.

A somatic cell hybrid mapping panel comprised of different cell lines was described by Joan Overhauser (Thomas Jefferson University, Philadelphia PA). This mapping panel divides the chromosome into 33 bins. All of the Genethon STRs, Utah STRs, and published genes have been mapped using this set of somatic cell hybrids (Rojas et al., 1993; Gerken et al., 1994; Rojas et al., 1995). A composite map containing this information was presented (Fig. 3).

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Fig. 3. The physical map of chromosome 18. Consensus physical maps are displayed next to an ideogram of human chromosome 18. FISH map: the localization of 60 cosmids (Nakashima et al., 1994) is depicted next to the ideogram. The cosmids are grouped into 8 regions relative to the standard banding pattern. Somatic cell hybrid map: The chromosomes have been divided into 26 bins using a deletion mapping panel of somatic cell hybrids. The approximate location of the deletion breakpoints are depicted by arrows. Column A contains markers that have not been ordered within the bin. Column B contains simple sequence repeats that have been ordered using linkage analysis. Column C contains markers that have been mapped to bins and ordered separately using radiation hybrids. For boxed markers see Fig. 2.

Fig. 2. Meiotic breakpoint map of chromosome 18. The grandparental phase-known obligate recombinant chromosomes detected for chromosome 18 in eight of the CEPH reference families are shown. The CEPH kindred, the sib in the kinship and whether the paternal or maternal chromosome carries the meiotic breakpoint is reported. The interval in the CHLC framework map where the meiotic breakpoint was detected is shown (also boxed in Fig. 3).

Center, San Antonio TX). The first panel was constructed after fusion of irradiated (7000 rads) HHW324 (human chromosome 18 only hybrid cell line) and ATSS549t cells. A total of 122 hybrids were isolated from this fusion. A second panel was constructed using 4000 rads with the same parental cell lines. A total of 83 hybrids was isolated. Forty-three markers from the 18q region were localized through the panel and a preliminary map was presented.
A set of 60 cosmids, physically mapped to chromosome 18 using fluorescent in situ hybridization (FISH) in conjunction with R- or DAPI-banding (Fig. 3), was described by Takashi Imamura (National Institute of Genetics, Mishima, Japan) (Nakashima et al., 1994).

An approach to develop complete STS-content based maps was presented by Ken Krauter (Albert Einstein College of Medicine, Bronx NY). The approach described utilizes the Quickmap-based Pooling Strategy (QPS) and has been worked out for the mapping of chromosome 12. With this pooling strategy, it has been shown that fewer than 60 PCR reactions are needed to identify all YACs containing a specific marker. The pooling strategy has been modeled for chromosome 18 and approximately 1800 YACs associated with chromosome 18 could be identified.

To generate an integrated physical map for the 18q-deletion syndrome region, Peter O'Connell (University of Texas Medical Center, San Antonio TX) described an approach that involves querying of the CEPH/Genethon Quickmap database using the least stringent confidence criteria (level 7). Approximately 600 YACs were identified and individually arrayed in 96-well plates. These YACs were tested for STS content with 90 distal chromosome 18q STSs. More than 250 YACs yielded positive signals for these STSs. The STS and YAC data were analyzed by Segmap and a linear order was inferred. Sixty-four STS markers were ordered into 10 multilocus contigs. These contigs were ordered and oriented using the chromosome 18 genetic map. It was estimated that these contigs span approximately 70% of the 18q21→qter region.

Progress in constructing a complete physical map of chromosome 18 by the Whitehead Institute/MIT Center for Genome Research was presented by Gary Silverman (representing Tom Hudson, Lincoln Stein and Eric Lander). Using STS-content mapping and the mega-size CEPH YAC...
library 22 contigs were assembled. As of the March 1994 release, the average number of YACs and STSs per contig are 23 (total = 521) and 8 (total = 184), respectively. They predict coverage of 90–95% of chromosome 18.

**Disease studies**

**Holoprosencephaly**

Holoprosencephaly is a common developmental defect of the forebrain and midface. Maximilian Muenke (Children’s Hospital of Philadelphia, Philadelphia PA) presented the characterization of 6 patients with 18p deletions and holoprosencephaly (HPE). The critical region for HPE could be narrowed to pter–18p11.3.

**Bipolar Affective disorder**

Two genetic linkage studies involving bipolar affective disorder (BP) were presented. Wade Berrettini (Thomas Jefferson University, Philadelphia PA) reported evidence for a pericentromeric locus in 22 bipolar kindreds, using affected sib-pair and pedigree-member methods (multipoint APM $P = 10^{-6}$). Colin Stine (John Hopkins University, Baltimore, MD) also reported affected sib-pair results supporting linkage to this same region ($P = 10^{-4}$). In addition, sib-pair and lod score results suggest linkage to 18q, near D18S38, but only when the disease is transmitted through fathers (multipoint lod score $= 3.54$ in paternal pedigrees). Candidate genes in the implicated regions include Golf and MC2R (18p), and N-cadherin and RED-1 (18q).

The characterization of the ACTHR gene as a possible candidate for BP was described by Sevilla Detera-Wadleigh (NIH, Bethesda, MD). An SSCP was previously identified in the 3' untranslated region of the ACTHR gene (18p11.2, Gantz et al., 1993). This polymorphism was used for the genetic localization of the gene. The following maps were derived using the CEPH pedigrees and 22 bipolar pedigrees: D18S53–7.8cM–ACTHR–5.9cM–D18S66–15.05 cM –D18S72 and D18S37–1.6 cM–D18S53–2.6 cM–D18S40–3.2 cM–D18S45–3.7 cM–D18S44–9.8 cM–D18S66. These results indicate that ACTHR is within the region of linkage significance to BP (Berrettini et al., 1994). Affected sib-pair analysis under the status model, which includes bipolars, schizoaffectives and unipolars as ill, gave a $P$-value of 0.023. The ACTHR gene in 22 unrelated bipolars is being sequenced to search for mutations.

**Niemann-Pick type C**

Niemann-Pick disease type C (NPC) is an autosomal recessive lipid storage disorder. Refined localization of the disease gene was discussed by Eugene Carstea (NIH, Bethesda MD). The NPC gene has now been mapped more precisely to between the markers D18S44 and D18S480 in band 18q11.

**Synovial sarcoma**

The t(X;18)(p11.2;q11.2) is the cytogenetic hallmark of human synovial sarcomas. A chimeric genomic fragment containing the breakpoint regions in X and 18 isolated through positional cloning (de Leeuw et al., 1994) was described by Ad Geurts van Kessel (University Hospital, Nijmegen, The Netherlands). In addition, a chimeric (X;18) cDNA clone was isolated (Clark et al., 1994) and the contributing genes were referred to as SYT (chromosome 18) and SSX (X chromosome). Subsequent sequencing of RT-PCR products from a series of synovial sarcomas revealed two alternative fusion products, SYT-SSX1 and SYT-SSX2, that relate to the occurrence of two different breakpoints in Xp11.2 (de Leeuw et al., 1995). These different breakpoints correlate with different histologies of the tumors, i.e. biphasic versus monophasic, respectively.

**Familial Cholestasis**

Two forms of familial cholestasis have been assigned to 18q21.3 through a search for shared segments, a linkage disequilibrium based approach (identity by descent). Benign recurrent intrahepatic cholestasis (BRIC) was localized through studies of Dutch pedigrees, as discussed by Roderick Houwen (Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands) (Houwen et al., 1994). Nelson Freimer (University of California, San Francisco CA) described the localization of a clinically distinct disorder, progressive familial intrahepatic cholestasis (PFIC) or Byler disease using samples drawn from the Amish kindred in which the disorder was first described (Carlton et al., in press). Through observation of recombinations, haplotype sharing among patients, and linkage disequilibrium between the disease and marker alleles, a likely candidate region encompassing both BRIC and PFIC has been identified between D18S64 and D18S60, a distance of less than 7 cM.

**Familial Expansile Osteolysis**

Familial expansile osteolysis (FFO) is a very rare autosomal dominant bone dysplasia. Anne Hughes (Queen's University of Belfast, Belfast, UK) reported that the localization of the gene has been refined to the region between D18S383 and D18S483 at 18q21.2–q21.3. A YAC contig of the region has been constructed.

**Colorectal Cancer**

A new homozygous deletion in a colorectal tumor that has been identified by representational difference analysis (RDA) was described by Traci Mansfield (Yale University, New Haven CT). This deletion spans a minimum region of 2.8 Mb and is located in 18q21.2–q21.3 which is additional to and does not include the DCC region in 18q21.1. Three expressed sequences have been identified by cDNA selection which map to this deleted region. One of these sequences represents the gene ERGIC-53, a 53-kDa membrane protein of the ER-Golgi intermediate compartment. A CEPH YAC
contig has been identified that spans the homozygous deletion.

Schizophrenia
Giorgio Sirugo (Yale University, New Haven CT) reported the detection by RED (Repeat Expansion Detection) of a very unstable (CTG)$_n$ dynamic mutation in a Danish schizophrenia kindred. However, other affected individuals from this kindred and from other Danish kindreds did not have significantly expanded (CTG)$_n$ repeats in their genome. The repeat was mapped to 18q21 by FISH.

Tourette Syndrome
Tourette syndrome (TS) is a neuropsychiatric disorder characterized by the childhood onset of motor and vocal tics. In an effort to identify a candidate TS gene, Leslie Boghosian-Sell (Thomas Jefferson University, Philadelphia PA) described a family with a t(7;18)(q22;q22.3) translocation which segregates with features of TS. A cosmid that spans the translocation breakpoint was described and several putative exons have been identified that map on either side of the chromosome 18 breakpoint region.

Transthyretin related hereditary amyloidoses
The transthyretin related hereditary amyloidoses (TTR HA) are a group of autosomal dominant diseases associated with missense mutations in the TTR gene, which maps to 18q12. These missense mutations (more than 40 discovered) cause TTR HA and show extremely variable phenotypes, including peripheral neuropathy, vitreous opacities and cardiomyopathy. Alessandra Ferlini (ITBA CNR, Milan, Italy) described a molecular analysis of 22 families. In 12 of these, the Met30 mutation was discovered, whereas in another six the Pro36, Ala47, Ala49, Leu64, Gln89 mutations were detected (Ferlini et al., 1992; Ferlini et al., 1994). Two new unreported missense mutations causing Thr34 and Ser125 substitutions were also described, the second one leading to an isolated cardiomyopathy. These findings indicate that the TTR gene is extremely prone to missense mutations, determining highly heterogeneous phenotypes.

18q- Syndrome
The breakpoints of 26 18q- cases were described by Gordon Stratdsee (Thomas Jefferson University, Philadelphia PA). This analysis was performed using chromosome 18-specific lambda phage cloning, which had previously been mapped to distinct regions of chromosome 18, as probes for FISH. A critical region for the 18q- syndrome mapping to the distal most portion of the long arm of the chromosome was defined. A YAC contig of this critical region containing one gap was also described.

A map showing the locations of diseases on chromosome 18 is shown in Fig. 4.
Gene Analyses

**G-olf α gene**

The G-olf gene is a member of the G-protein family. The human G-olf α gene is located on chromosome 18p11, a region that has been linked to bipolar illness in some of the families (Berrettini et al., 1994). The human chromosome 18-specific cosmid library (Lawrence Livermore National Laboratory, CA) was screened with human G-olf α cDNA probes. Fifteen cosmid clones were obtained that span the gene. Regions containing all 12 exons were sequenced and described by Leena Ala-Kokka (Thomas Jefferson University, Philadelphia PA).

**Cadherin gene family**

The desmogleins (DSG) and desmocollins (DSC) are members of the cadherin superfamily of calcium-dependent adhesive glycoproteins. Joachim Amemann (Institute for Human Genetics, Frankfurt, Germany) described the genomic organization of 6 members of this superfamily and determined the order: (DSG2-DSG3-DSG1-DSC1-DSC2-DSC3) (Simrak et al., 1995). Transcription of the gene clusters occurs in opposite directions, suggesting the presence of a shared locus control region in-between the two clusters.

**Regulatory Light Chain Genes**

Analysis of two regulatory light chain genes (RLCA and RLCB) performed by Akinori Kimura (Tokyo Medical and Dental University, Tokyo, Japan) was presented by Joan Overhauser. The two genes were isolated based on the homology to rat cDNA clones. Two transcripts were identified for the RLCA gene. One transcript was ubiquitously expressed, while the other transcript, a result of alternative promoter usage, was muscle-specific. The potential involvement of these genes in familial hypertrophic cardiomyopathy (FHCム) was discussed.

**Serpin gene family**

Four members of the serine proteinase inhibitor (serpin) family mapping to 18q21.3 were described by Gary Silverman (Harvard Medical School, Boston MA). MASPIN, squamous cell carcinoma antigen 2 (SCCA2), squamous cell carcinoma antigen 1 (SCCA1) and plasminogen activator inhibitor type 2 (PAI2/PLANH2) are oriented centromeric to telomeric, respectively, within a 300-kb interval (Schneider et al., 1995). This interval maps 300 kb telomeric to BCL2. Three of the serpin, (MASPIN, SCNA2, and SCCA1) are contained within a single YAC, yB29F7. PAI2 is contained within YACs yA27D8, yA24E4, and yA211F5.

**Other Genes**

A fifth melanocortin receptor (MCR5) (Chowdhary et al., 1995), two transcription factors, NFATC1 and NFATC2 (Li et al., 1995), and a cell membrane, oligomeric metalloendopeptidase, MEP1B (Bond et al., 1995), were mapped to chromosome 18.

**Comparative Mapping**

The relationships between human chromosome 18 and the mouse genome were presented by David Kohrman (University of Michigan, Ann Arbor MI) (Fig. 5). Most genes mapped to human chromosome 18 are located within a proximal (~10 cM) and a distal (~ 20 cM) cluster of genes on mouse chromosome 18 (Fig. 5). The proximal and distal clusters correspond to the human 18q11→q12 and 18p11→q23 regions, respectively. Small segments on mouse chromosomes 1 and 17 contain regions syntenic to the human BCL2-PLANH2 locus at 18q21.3→q22 and the LAMA1 loci at 18p11, respectively.

Two mouse mutations, Twirler (Tv; dysplasia of the nasal bones, cleft palate, labyrinthine hypoplasia and obesity) and ataxia (ax; progressive paralysis) map ~3 cM from the centromere (Griffith et al., manuscript in preparation). Microsatellite markers developed from corresponding human lambda clones mapped to 18q11 by FISH, genetic linkage using the CEPH pedigrees and or somatic cell hybrid panels. Other mouse mutants with homologs predicted to reside on human chromosome 18 are balding (bail; hair loss, immunologic defects), sphingomyelinosis (spn; progressive ataxia, a possible model for NPC), shaker-with-syndactyly (sy; deaf, circler, degeneration of membranous labyrinth), chronic multifocal osteoyelitis (cmo; bone inflammation) and shiverer (shi, mutation of the myelin basic protein).

**Resources**

**Cell Lines**

A panel of somatic cell hybrids that allows for the regional mapping of a marker to one of 6 subregions is available from the Coriell Institute (Markie et al., 1992; Kline et al., 1992; Rojas and Overhauser, 1993; Overhauser et al., 1993). Also available from the Coriell Institute is a number of lymphoblastoid cell lines containing deletions of the long arm of chromosome 18.

Genomic DNAs from the somatic cell hybrid deletion mapping panel described by Joan Overhauser are available for PCR mapping. Contact: J. Overhauser (Thomas Jefferson University, Philadelphia PA).

The monochromosomal hybrid cell lines, MS/26-21 (chromosome 18 only) and MS/26-7 (18p only) are currently available to collaboration in the form of genomic DNA.
Fig. 5. Comparative linkage map of human chromosome 18 genes localized in the mouse. Approximate distances from the centromere are indicated in cM. Mouse chromosome 18 genes localized by in situ hybridization or somatic cell hybrid analysis are boxed. Genes mapped in human are underlined, with human locations at left. Mutant loci are shown in bold. This map has been adapted by D. Kohrman and M. Meisler from the 1994 Chromosome Committee Report (Johnson and Davisson, 1994), and other references (Goldstein et al., 1994; Masquillier et al., 1993; Ishikawa et al., 1994; Bond et al., 1995; Li et al., 1995). Microsatellite, viral integration sites, and other anonymous markers have been omitted. References are available from the Mouse Genome Database (MGD) via the Internet (Table I).

(Radiation-reduced somatic cell hybrids for mapping purposes are presently being screened. Contact: R. Leach (University of Texas, San Antonio, TX).

Databases

Jamie Cuticchia discussed the role of the Genome Data Base (GDB). A demonstration of how to obtain information from GDB was provided.

Information is available from a number of databases accessible through the world wide web (WWW). Table I lists the databases that may be helpful in accessing information on the physical and genetic maps of chromosome 18.

A chromosome 18 home page will be generated as a result of this workshop and will be made available at the Utah representative's WWW home page or Steve Gerken (University of Utah, Salt Lake City, UT).
A list of useful WWW sites for obtaining chromosome 18 information is presented in Table I.

**Future chromosome 18 workshops**

It is anticipated that the physical maps of all human chromosomes will be completed in the near future. However, chromosome 18 lags behind several others because of the absence of a chromosome 18 Human Genome Center. It is expected that with the availability of large series of chromosome 18-specific YACs and efforts to generate integrated maps, completion of the physical map will be facilitated by another chromosome 18 workshop in a year.

Preliminary plans are to organize the fourth international workshop on human chromosome 18 mapping in Boston, MA USA. Contact: Gary Silverman (Harvard Medical School, Boston MA; telephone: 617-355-6416; fax: 617-355-7677; e-mail: SILVERMAN_G@A1.TCH.HARVARD.EDU).

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A PCR-based genetic linkage map of human chromosome 18 (G00-592-404)

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The gene for the g-protein G-olf a tissue specific expression as mRNA with variable length 3’-non-translated regions (G00-592-397)

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A YAC contig for the desmosomal cadherin locus at 18q12.1 (G00-592-403)

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A linkage study of bipolar illness (G00-592-385)

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Characterization of a (7;18) chromosome translocation breakpoint that segregates in a family with features of Tourette’s syndrome (G00-592-406)

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A genetic map of human chromosome 18 (G00-592-409)

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Localizing the human Niemann-Pick disease type c gene to 18q11 (G00-592-395)

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The role of the Genome Data Base at the chromosome 18 workshop (G00-592-393)

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Identification of two alternative fusion genes, SYT-SSX1 and SYT-SSX2, in t(X;18)p11.2;q11.2)-positive synovial sarcomas (G00-592-386)

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Candidate genes for bipolar illness on chromosome 18 (G00-592-400)

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Fine mapping of a locus for familial cholestasis in 18q21 (G00-592-405)

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Comparative mapping of a disease gene linkage marker on human and mouse chromosome 18 (G00-592-396)

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The BRIC gene is localized between the markers D18s69 and D18s60 (G00-592-390)
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Physical mapping of the familial expansile osteolysis region in chromosome 18q21.3 (G00-592-401)

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Isolation, characterization and mapping of a human RIC gene family on the short arm of chromosome 18 (G00-592-411)

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An integrated physical map of human chromosome 12 (G00-592-394)

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Radiation-reduced hybrid panel for human chromosome 18. (G00-592-399)

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Loss of heterozygosity on chromosome 18q in a colorectal cancer (G00-592-391)

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Definition of the holoprosencephaly minimal critical region (MCR) on chromosome 16p (G00-592-410)

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Construction of human chromosome 18 cosm id library and mapping of 60 new probes using fluorescence in situ hybridization (G00-592-387)

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STS content-based YAC map of distal long arm of human chromosome 18 (G00-592-396)

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Somatic cell hybrid mapping panel for chromosome 18 (G00-592-407)

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Transthyretin (TTR) gene: Identification of new mutations and genotype-phenotype correlation (G00-592-402)

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A family of human serine proteinase inhibitors map to 18q21.3 (G00-592-388)

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Repeat expansion detection (RED) of a (CTG)n dynamic mutation in a Danish schizophrenia kindred, mapped to chromosome 18q21 by in situ hybridization. (G00-592-392)

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Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect (G00-592-389)

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Molecular cytogenetic analysis of 18q-syndrome (G00-592-408)