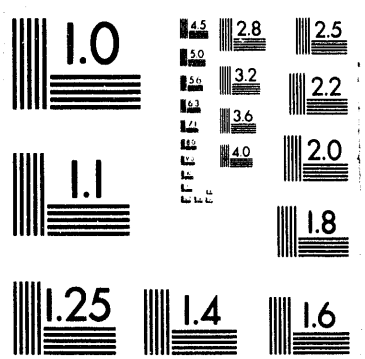
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1 of 1

Report of the Fourth International Workshop on Human X Chromosome Mapping 1993

David Schlessinger, Jean-Louis Mandel, Anthony P. Monaco,
David L. Nelson, and Huntington F. Willard, Editors

Introduction

Vigorous interactive efforts by the X chromosome community have led to accelerated mapping in the last six months. Seventy-five participants from 12 countries around the globe contributed progress reports to the Fourth International X Chromosome Workshop, organized by D. Schlessinger, J-L. Mandel, and H.F. Willard at St. Louis, MO May 9-12, 1993. It became clear that well over half the chromosome is now covered by YAC contigs that are being extended, verified, and aligned by their content of STSs and other markers placed by cytogenetic or linkage mapping techniques. At the meeting and for the convenience of readers of this report, discussions focussed both on global approaches to genetic and physical mapping of the entire X and on more specific, targetted efforts in four subregions. The major aim of the workshop was to assemble the consensus map that appears as Figure 1 in this report, summarizing both consensus order and YAC contig information. Tables 1 and 2 list breakpoints and genes according to the consensus map. Comparative genetic maps are represented in Figure 2, along with a listing of microsatellite markers in Table 3. Supporting information is indicated in references listed in this report and in the appended abstracts from the meeting. The availability of resources, such as somatic cell hybrids, YACs, STS sequences, and probes, is indicated in the references or in previous reports (Mandel et al., 1992, 1993). In general, though, a condition of the meeting was that resources presented in abstracts and posters were considered to be publicly available.

This summary partially updates the report of the Chromosome Coordinating Meeting (CCM92) (Mandel et al., 1993) and Mandel et al. (1992) in the context of the discussions at XCW4, and should be considered tentative in the sense that much of the data have not been published. A more complete report will be prepared for CCM93.

Overall physical and genetic mapping, and corresponding informatics

As further summarized below, many groups, including CEPH/Genethon (Paris), the Human Genome Centers at Baylor College of Medicine (Houston) and at Washington University (St. Louis) and the laboratories of Bentley at Guy's Hospital, Lehrach at ICRF, and Monaco at Oxford, have contributed extensively to the development of YAC contigs in a number of regions, and also, in more delimited regions, to supplementary mapping in cosmids. In the most extensive efforts, the Baylor group reported on an intensive study of the telomere-proximal portion of Xp and the Washington University Center reported that using STS content mapping with 712 STS's, the 100 Mb of Xpter-q24 has now reached about 65% coverage in contigs of average size 0.7 Mb. In collaboration with the group of D'Urso in Naples, the St. Louis group also reported refinements of the map in the 50 Mb region of Xq24-qter, which is now more than 95% covered. The Monaco group reported more than 50% coverage of the proximal long arm, from the centromere to Xq13, while Bentley and colleagues presented a contig of much of the Xq22 band.

Contig assembly continues to be based on a variety of methods using STS content and hybridization probes. In addition to strategies like all-walking methods with YAC end-inserts (Kere et al., 1992), Cole et al. (1992) have used random STSs to recover YACs for defined chromosomal regions, and that group and others [e.g., Muscatelli et al. (1992) and Freije and Schlessinger (1992)] have used Alu-PCR products from YACs, somatic cell hybrids, or radiation hybrids, to screen reference libraries and detect overlaps. Cooke reported further characterization of a telomere-fragmentation hybrid panel for Xq (abs. 18). Some clustering of breaks is observed towards the centromere (even within the DXZ1 locus). Sequences at the breakpoints can be recovered for use as markers. A single copy probe

bank was also suggested as a route to the recovery of overlapping YACs by hybridization methods (abs. 14).

The contig results from many groups are now being integrated by the use of STSs and linkage probes that are in common (and sometimes by the use of YACs retrieved from the same libraries). Figure 1 shows the coverage of the chromosome overall by YAC contigs that are generally more than 1 Mb long and are positioned and at least partially ordered within cytogenetic regions.

Physical mapping is now reaching the phase of "closure" in most regions of the chromosome. It is a truism, however, that the last 10% of the map can require 90% of the effort, with contigs presenting a variety of problems requiring investigation on a case-by-case basis. Challenges that were illustrated at XCW4 were posed by regions that are unstable, recombined, or unrecovered in cloned DNA; problems caused by sequence elements that are repeated along the X; clones that contain large internal deletions or bring together cloned fragments from disparate regions of the X; and other discrepancies in the map. A number of aids to orientation and alignment of contigs were presented, including an extension of the approach of telomere fragmentation to define intervals along Xq (abs. 18), the development of a panel of DNAs from patients with overlapping deletions or translocated regions (abs. 3, abs. 21), and the use of fluorescence *in situ* hybridization (FISH) to discriminate and order probes either in interphase nuclei or along metaphase chromosomes (abs. 1, abs. 45).

A major aid to closure, and of course a major route to the finding of disease genes, is the corresponding genetic map. Mulley (abs.49) reported the characterization of 7 new microsatellites (DXS1120, DXS1122-1226, DXS1156), genotyping of those and 13 other such markers in the 40 CEPH reference pedigrees, and construction of a PCR-based genetic map, suing also data on other markers in the CEPH database (notably those of Weissenbach et al., 1992). A 236 cM framework map was thus obtained, incorporating 30 loci from the XG blood group locus to DXS52; 30 other marekrs could be uniquely ordered with sufficient statistical support, although several can be orfered from physical mapping or other linkage studies. Another framework map with 32 loci (mostly microsatellites) was constructed by the consortium effort of Murray et al. (abs. 52), covering 210 cM from DXS143 to DXS15. Both maps are presented in Figure 2, along with coordinates for markers in common with the maps of Fain and Barker (XCW3 and CCM92 report) and Weissenbach et al. (1992). The maps are in good overall agreement. Differences in genetic distances are, however, seen in some regions -- in particular, Xp22 and Xq22-q26; and the genetic length between DXS143 and DXS52/DXS15 is 210, 205, and 173 cM in the maps of Murray et al., Mulley et al. and Fain and Barker, respectively (and can be extrapolated to about 180 cM for the map of Weissenbach et al., 1992).

Refined genetic mapping in selected regions has revealed hot spots of recombination at the Xp telomere (Rappold et al., abs. 6) and in two regions of the dystrophin gene (DMD; Oudet et al., 1992). The genetic map was extended towards the Xq telomere by isolation of a CA repeat mareker (DXYS154) from the Xq-Yq homologous region which covers 400 kb at the distal end of Xq28. This marker (3 cM distal to DXS52) was shown to recombine between X and Y in about 2% of male meioses, and thus defines a new pseudoautosomal region (Freije et al., 1992). Many microsatellite markers are now unambiguously placed within ordered contigs (starred in Figure 1). Those characterized since the last update in the CCM92 report are underlined in the ordered list of Table 3.

STS-based mapping of the mouse X chromosome is underway using YAC libraries from ICRF and St. Mary's (the latter in a rad52 host; abs. 11). The synteny between the mouse and human X chromosomes extends over most of the chromosome, in at least eight identifiable segments (abs. 2, 9, 10, 11, 36).

For functional mapping of the genome, the approaches presented utilized the general recovery of a group of X-specific cDNAs by hybridization of pools of arrayed cDNAs against chromosome-specific cosmid arrays (abs. 13); and variants of direct selection using either YAC or cosmid clones, including the use of hybridization of genomic clones of one species against cDNAs of another species (abs. 6, abs. 58). A number of laboratories are also verifying contigs and initiating searches for genes by structural studies. The studies often include rare-cutter restriction enzyme mapping to identify putative CpG islands, but for the first time, four discussions (abs. 15, 32, 55 and 61) also pointed toward functional mapping by the inference of gene content in extensive sequence tracts (see section on Xq24-qter).

In the next three years, groups led by J. Sulston, E. Chen, R. Gibbs, D. Bentley, M. D'Urso, and A. Rosenthal all expect to sequence 2 to 3 Mb of DNA, including the CV-L1CAM region

(Sulston/Rosenthal) and Xq22 region (Sulston/Bentley), the CV-G6PD and EDA regions (Chen/D'Urso), and the region from FMR1 toward IDS/DXS304 (Gibbs). These studies would make the X chromosome a major target of human genome sequencing efforts.

Several reports dealt with ways to enter, represent, and communicate data and maps. In addition to the discussion of the latest version of the Genome DataBase, discussions of alternative and/or complementary integrated databases were given by Lehrach's group (including results of the use of hybridization of probes to distributed gridded filters) (abs. 62, 63) and Morton's group (including weighted genetic and physical data)(abs. 48). Demonstrations were also provided of SEGMAP, a program of P. Green and C. Magniss (Washington University), that uses information about YAC size and STS content to generate maps and indicate inconsistencies, and Sigma, a program from J. Fickett and M. Cinkosky (Los Alamos National Labs), a graphical interface that can be used to represent, edit, and save maps inferred from database and laboratory entries.

Cloned disease genes and newly assigned genes

The cloning of X-linked genes is continuing at an increasingly rapid pace. Since the CCM92 report, positional cloning or candidate gene approaches have led to the identification of the disease genes for Bruton's agammaglobulinemia in Xq22 (AGMX1, coding for a tyrosine kinase called ATK, Vetrie et al., 1993; Tsukada et al., 1993), adrenoleukodystrophy (ALD, Mosser et al., 1993), glycerol kinase deficiency (GK, Sargent et al., 1993; Walker et al., 1993), immunodeficiency with hyper-IgM (HIGM1, corresponding to the CD40 ligand CD40L, Allen et al., 1993; Aruffo et al., 1993; DiSanto et al., 1993; Korthauer et al., 1993), and severe combined immunodeficiency (SCIDX1, identified as the IL2RG gene, Noguchi et al., 1993; abs. 94). The monoamine oxidase A gene (MAOA) was shown to be implicated in a family with X-linked borderline mental retardation and prominent behavioral disturbance (Brunner et al., 1993, and B. Van Oost, personal communication). This striking finding suggests that candidate gene approaches may be efficient to identify mutations in families with syndromal or non-syndromal ("non-specific") forms of X-linked mental retardation. Isolation of candidate cDNAs or trapped exon sequences were reported at the Workshop for ectodermal dysplasia (EDA, abs. 39 and 93), McLeod syndrome (XK, abs. 47), and for a gene in Xq13.1 interrupted by an X;13 translocation associated with mental retardation in a single female (abs. 21). YACs that cross synovial sarcoma translocation breakpoints in Xp11.21 have been isolated by Knight et al. (1992) and deLeeuw et al. (1992). A third fragile site in Xq27.3-q28 (FRAXF) was identified in a single family, lying distal to FRAXA and FRAXE, between DXS479 and DXS305/374. It may be less folate-sensitive than FRAXA and FRAXE (Hirst et al., 1993).

Regional localizations based on linkage analysis have been reported for previously unmapped X-linked diseases, including X-linked cutaneous amyloidosis in Xp22-p21 (suggested symbol RPD, abs. 51), X-linked nephrolithiasis in Xp11.22 (XRN, abs. 77), X-linked variable pan-hypopituitarism in Xp21.1-p11.2 (PHP, Lagerstrom et al., abs. 36 in XCW3), the Simpson-Golabi-Behmel malformation syndrome in Xcen-q21.3 (SDYS, Hughes-Benzie et al., 1992), X-linked alpha-thalassemia and mental retardation in Xq12-q21.3 (ATRX, Gibbons et al., 1992), and split-hand/split-foot anomaly in Xq25-q26 (ul Haque et al., 1993). A gene which modulates fetal hemoglobin levels and which may escape X-inactivation was mapped to Xp22.2 by linkage to DXS85 and DXS43 (z=4.6, Dover et al., 1992). Precise localization of a translocation breakpoint giving rise to Aarskog syndrome (FGDY) in Xp11.21 is consistent with genetic mapping data (abs. 33 and 71, Porteous et al., 1992). The association of Alport syndrome, leiomyomatosis and congenital cataract (OMIM 308940) may represent a new contiguous gene syndrome, as 3 patients analyzed all had deletions extending beyond the 5'end of the COL4A5 (Alport syndrome) gene (Antignac et al., 1992).

Linkage analysis in families with various forms of X-linked mental retardation is being actively pursued [see Neri et al., 1992, and Mulley et al., 1992, for reviews, and reports by Arena et al., 1992; Bialer et al., 1992; Jedele et al., 1992; Kerr et al., 1992; Mathews et al., abs. 53; Nordstrom et al., 1992; Saugier-Veber et al., 1993; Schwartz et al., 1992 and abs. 70; Wilson et al., 1992). Other localizations of genes involved in mental retardation are derived from analysis of patients with translocations or large deletions (Bach et al., 1992; Ballabio et al., 1992 and abs. 21). Several newly cloned genes have been assigned to X, including genes coding for enzymes (ANT3 ADP/ATP

translocase and ASMT acetyl serotonin methyl transferase in the pseudoautosomal region, SSAT spermidine/spermine acetyl transferase in Xp22.1), for interleukin receptor subunits (IL3RA in the pseudoautosomal region, IL2RG in Xq13), receptors for glutamate (GLUR3) and serotonin (HTR1C) in Xq24-q25, a ligand for the CD40 receptor (CD40L, in Xq26), homologs of drosophila heterochromatin proteins (HSMXS in Xp22.1 and HSMXL in Xq11.2-q12) and proteins with zinc finger motifs in Xp11 (ZNF21, ZNF81, ZXDA, ZXDB), in Xq26 (ZNF75), and in Xq28 (HZF22).

Many of the genes mentioned above are discussed further in the relevant regional sections below and placed on the map in Figure 1.

Xpter to Xp21.3

Significant acceleration of mapping progress has occurred in this region. Beginning with the pseudoautosomal region at Xpter and moving proximally to the AMELX locus, there is a very nearly complete physical map based on YAC contigs, chromosome breakpoints and pulsed-field mapping (PFGE). Clarification of map order and generation of several YAC contigs of significant size in the more proximal regions of Xp22 has also occurred. Several new or newly localized genes have also been described. The consensus map of the region is provided in figure 1.

The recently described YAC contig of the human Y chromosome provided a physical map of the X-Y shared, 2.6 Mb pseudoautosomal region (PAR) based on YACs and STSs (Foote et al., 1992). This work has recently been supplemented by efforts by Petit and coworkers (abs. 92), (Slim et al., 1993a), involving generation of 25 novel STSs and identification of 31 YACs. Five of the six known genes in the pseudoautosomal region were positioned on the contigs (figure 1) and the PFGE map (abs. 59, abs. 92; Rappold et al., 1992; Schiebel et al., 1993; Slim et al., 1993b; Smith et al., 1993; Milatovich et al., 1992). Two of these, hydroxy-indole O-methyl transferase (HIOMT) [also called ASMT for acetyl serotonin methyl transferase] and IL3RA (interleukin 3 receptor alpha subunit), have recently been shown to map to the PAR. ASMT (Yi et al., 1993) is approximately 1.5 Mb from the telomere (figure 1), while IL3RA is within 50 kb proximal to CSF2RA at 1200 kb from the telomere (Milatovich et al., 1992). A fifth PAR gene (XE7) has recently been characterized (Ellison et al., 1992a; Ellison et al., 1992b), appears to encode a nuclear protein, and is thought to be localized in the proximal half of the region (abs. 26), but has not yet been placed on the YAC contig.

Rappold et al. (abs. 6) constructed a genetic map for 11 pseudoautosomal loci precisely positioned on the physical map. The overall recombination frequency is 10-fold higher in male than in female meiosis, except for the most telomeric 80 kb. That interval showed comparable recombination rates in males and females, and constitutes a recombination hotspot, with a 30-fold higher rate than expected from its physical extent.

Moving proximally within Xp22.3 from the pseudoautosomal boundary, Ballabio and coworkers described a breakpoint map based on 60 STS markers (40 of them new), defining 32 intervals with 150 associated YACs between the PAR boundary and PHKA2 (abs. 3), (Schaefer et al., 1993). Breakpoints are largely derived from patient cell lines and hybrids, and these provide localization of disease phenotypes on the physical map as well (Ballabio and Andria, 1992). Zoghbi (abs. 87) described refinement of the positions of the genes involved in ocular albinism (OA1) and microphthalmia with linear skin lesions (MLS) based on deletion mapping, along with a 2.6 Mb, 19 YAC contig and restriction map in the interval from DX143 through AMELX (Wapenaar et al., 1993). These maps, added to those of the distal 10 Mb from the telomere to DXS143 derived by genomic pulsed-field mapping (Petit et al., 1990), and a YAC contig-based map of the region between GS1 (Yen et al., 1992) and KAL, provide a detailed physical map of the distal 13 Mb of the short arm of the X chromosome (figure 1). The AMELX gene has been firmly established as involved in some but not all families with X-linked Amelogenesis Imperfecta (Aldred et al., 1992a; Aldred et al., 1992b; Bailey et al., 1992; Salido et al., 1992).

Proximal to DXS143, the map becomes much less well-defined, although significant progress was reported by several groups in filling in this region of Xp22.1 to p22.2. Several YAC contigs were reported. Parallel efforts reported by Alitalo et al. (abs. 1) and Hanauer (abs. 35) aimed at the region between DXS16 and DXS43, encompassing the reference marker DXS207 and the Weissenbach CA repeats DXS987 and DXS1053 in an approximately 3 Mbp region. The Alitalo contig consists of 40

YACs spanning 3.4 Mb with a single gap between the glycine receptor alpha (GLRA2) gene and DXS207, and six novel STSs as well as a new polymorphic tetranucleotide repeat at DXS207. The order pter - DXS16-DXS9-GLRA2-DXS207-DXS197-DXS43 - cen is supported by both FISH ordering and by a chromosome breakpoint separating DXS207 and DXS43 (Monaco, unpublished). Hanauer reported that the Weissenbach microsatellite AFM164zd4 (DXS1053) is found in a 900 kb YAC along with DXS43, DXS197, and DXS207. He suggested the order DXS16-DXS43-DXS1197-DXS207-DXS1053, based on analysis of YACs and on one meiotic crossover (abs. 35), at variance with the order of Alitalo et al.

The XE59 gene and Weissenbach microsatellite DXS987 are also located in this region, and are placed in the interval between breakpoints BXP56 and BXP57,58 in the deletion map (abs. 3) (Schaefer et al., 1993), along with DXS69, DXS414, and DXS418.

Refinement of the location of the Coffin-Lowry syndrome (CLS, between DXS999 and DXS274) was reported by Hanauer (abs. 35), and tight linkage between retinoschisis (RS) and DXS207 was confirmed (Oudet et al., 1993). Hors-Cayla (abs. 37) presented evidence that the SEDL gene is located between DXS16 and DXS92. Boyd (abs. 10) reported localization of the gastrin-releasing peptide receptor gene (GRPR) to the interval between Pdha-1 and Amg in the mouse and in the Xpter-p21.1 region of the human X, suggesting a location proximal to AMELX. A newly localized gene with the provisional acronym SSAT (spermidine/spermine N1-acetyl transferase) has been placed in Xp22.1 (Xiao et al., 1992). A location in Xp22.13 was reported for a chromobo.. ntaining gene (designated HSMXS), which shows homology to a drosophila gene implicated in position-effect variegation, and is the likely homology of the *Cbx-rs1* mouse gene (Reik et al., 1992).

YAC contigs in the interval containing DXS365 and DXS274 were reported in pursuit of the HYP gene (abs. 64, 65; Econs et al., 1992). A 12 YAC contig of 1.5 Mb contains DXS365, DXS274 and DXS41, which can be represented in a minimal set of three YACs (abs. 65), and these YACs were also identified by Alu-PCR screening using a radiation hybrid-derived complex probe (abs. 5) (Benham and Rowe, 1992). Rowe's linkage analysis places HYP most probably in the interval between DXS365 and DXS274 and further indicates that DXS999 is distal to DXS365 and HYP (abs. 64). Another Weissenbach microsatellite, DXS1052, was found by Rowe to be contained on a 1200 kb YAC with DXS274.

A collection of linking clones created with Eag I and Not I was described by Thakker (abs. 77); four of these mapped to Xp22. Den Dunnen described identification of 40-50 YACs from a CEPH/Genethon X-specific sublibrary, using probes derived from the distal p arm (23). These will be integrated with the existing physical maps, and should provide significant coverage of the region.

The gene involved in X-linked cutaneous amyloidosis was localized with microsatellite markers to Xp22-p21 by Mulley (abs. 51), and the name reticulate pigmentary disorder with systemic manifestations (RPD) was suggested.

Although not presented at the workshop, additional interesting data regarding other genes in the region have been described since the CCM92 report (Davidson et al., 1992; del Castillo et al., 1992; Guioli et al., 1992; Hardelin et al., 1993; Hardelin et al., 1992; Hendrickx et al., 1993; Incerti et al., 1992; Li et al., 1992; Oosterwijk et al., 1992; Reik et al., 1992; Wauters et al., 1992). Some of the data presented in these papers are included in figure 1.

Xp21.3 to Xp11.1

In Xp21.3 the genes for zinc finger X (ZFX) and DNA polymerase alpha (POLA) have been linked on a 1.5 Mb YAC contig (abs. 5) within less than 750 kb, similar to results reported from a 1.4 Mb YAC contig in the mouse (Hamvas et al., 1993). One of the two radixin pseudogenes (RDXP2) has been mapped by somatic cell hybrids and patients with deletions to Xp21.3 (Wilgenbus et al., 1993). It has been further localized near DXS68 in the 1.1 Mb YAC contig previously reported to contain DXS68, DXS67, DXS669 and DXS28 (abs. 47, Walker et al., 1991).

The 3.2 Mb YAC contig containing the complete DMD gene (Monaco et al., 1992, Coffey et al., 1992) has been extended in both directions for a total of 4.4 Mb. Distally, the contig was connected to DXS708 and shown by deletion analysis to contain the genes for adrenal hypoplasia congenita (AHC)

and glycerol kinase deficiency (GK). Several new anonymous DNA probes have been generated and ordered by deletions and YAC clones in this region (abs. 47, Walker et al., 1992; Worley et al., 1992; Worley et al.,1993). The gene for GK was recently isolated by two groups and shown to have strong homology to bacterial GK genes (Sargent et al., 1993; Walker et al., 1993).

In Xp21.1, several groups have isolated YACs (abs. 28, abs. 47, Ho et al., 1991) containing McLeod syndrome (XK), chronic granulomatous disease (CYBB), retinitis pigmentosa 3 (RP3) and ornithine transcarbamylase (OTC). The largest contig extends for 1.7 Mb and cosmid contigs underlying several of these YACs are being used to search for candidate genes for XK and RP3 (abs. 28, abs. 47). Two new microsatellite polymorphisms have been reported, one near the BB deletion breakpoint (DXS1110) and one near OTC (pOCP1; abs. 28).

In Xp11.3, the previously reported YAC containing DXS7, monoamine oxidase A and B (MAOA, MAOB) and Norrie disease (NDP, Berger et al., 1992; Chen et al., 1992), has been extended proximally by two groups (abs. 19, abs. 20) to a length of 1.3 Mb and shown to contain the locus DXS742 (Bergen et al., 1993) and a third pseudogene for ribosomal reductase (RRM2P3). The YAC contig in Xp11.23 containing the genes for murine sarcoma viral oncogene homolog (ARAF1), synapsin1 (SYN1), tissue inhibitor of metalloproteinase (TIMP), properdin P factor (PFC) and DXS426 (Coleman, et al., 1991; Derry & Barnard, 1992) has been extended by several groups to about 1.7 Mb to include the ETS-related gene ELK1 (abs. 42), the zinc finger genes ZNF21 and ZNF81(abs. 42), the distal ornithine aminotransferase-like sequence cluster (OATL1, abs. 17, abs. 42, abs. 43) and the polymorphic locus DXS1003 (abs. 17). One group reported extension of the contig distally to include UBE1, about 300 kb from ARAF1 (abs. 43), although this observation may be inconsistent with other data (abs. 17) and requires confirmation. In Xp11.22, the genes for synaptophysin (SYP) and transcription factor binding to IGHM enhancer 3 (TFE3) have been localized on a 420 kb YAC (abs. 43). Other genes and loci in Xp11.23-11.22 have been isolated in YACs but have not yet been connected to the two large contigs. The overall consensus order (Figure 2) is pter-OTC-DXS209-DXS228-DXS77-DXS7-MAOA-MAOB-NDP-RRM2P3-DXS742-UBE1-DXS1003-ARAF1-3'SYN1-TIMP-5'SYN1-DXS426-PFC-EKL1-ZNF21-ZNF81-OATL1-(DXS226,GATA1)-SYP-TFE3-DXS255-DXS146-cen. The location of genes involved in retinitis pigmentosa 2 (RP2) and congenital stationary night blindness 1 (CSNB1) have been broadened compared to the last report, based on re-evaluation of genotyping data in critical families, and now have limits between MAOB and DXS255 (abs. 17 and unpublished results).

In Xp11.21 there has been extensive work by several groups to map and order loci (Gorski et al., 1992; Laval and Boyd, 1993; Greig et al., 1992; abs. 84) and to construct YAC contigs. The two CEPH microsatelite markers DXS1000 and DXS988 have been mapped to interval number 4 (interval map of Lafreniere et al., 1991), the same one as OATL2 (abs. 84), which is consistent with radiation hybrid mapping (abs. 4). Knight et al. (1992) has shown that two YACs containing the proximal OATL2 cluster cross a synovial sarcoma translocation breakpoint. Interestingly, YACs for the more distal OATL1 cluster were shown by de Leeuw et al. (1992) to cross a second synovial sarcoma translocation indicating that perhaps there are two synovial sarcoma loci which may have duplicated with the OATL sequence cluster. A YAC for DXS423E was shown to cross the translocation breakpoint (abs. 84) which defines the border between intervals 4 and 5 in the map of Lafreniere et al. (1991). A translocation giving rise to Aarskog syndrome (FGDY) has been localized between the flanking markers DXS323 and the delta-aminolevulinate synthase gene (ALAS2) (abs. 33). This is consistent with genetic linkage analysis giving a location for FGDY in Xp11.2-q12 (abs. 71; Porteus et al., 1992).

Gorski et al. (1992; abs. 33) have used radiation hybrids, somatic cell hybrids, translocations related to FGDY and incontinentia pigmenti (IP1), PFGE mapping in genomic DNA, and YAC clones to derive an order of markers in Xp11.21 as pter-DXS323-FGDY t(X;8)-ALAS2-DXS741-IP1 t(X;13) & t(X;9)-DXS705-DXS706-MTHFDL1-DXS370-DXS14-DXS740-DXS343-DXS422-IP1 t(X;17)-DXZ1. This is consistent with and extends previous orders in this region, as summarized in previous reports. An approximately 2.0 Mb YAC contig has been constructed containing the ALAS2 gene and the conserved markers DXS679 and DXS674 (abs. 9). YAC contigs centered around the locus DXS14 have been constructed by two different groups (abs. 9; abs. 84). The conserved locus DXS390 seems to be represented as two loci flanking DXS14 in one YAC contig (abs. 9) and may correspond to the duplicated zinc finger genes (ZXDA and ZXDB) isolated in the second DXS14 contig (Greig et al.,

1992; abs. 84). By combining data on the genes and loci used in common by the different laboratories the following consensus map is determined: pter-DXS146-(DXS1000, DXS988, OATL2)-DXS423E-DXS323-(ALAS2, DXS679, DXS674, DXS741)-DXS705-DXS706-MTHFDL1-DXS429-DXS390/ZXDB-DXS14-DXS390/ZXDA-DXS422-DXZ1.

Radiation hybrid resources were also presented for the Xp11 region by several groups (abs. 4, abs. 20, abs. 33). These helped in ordering loci in conjunction with YAC and PFGE data and will continue to be a valuable resource to help position new markers in the region, in conjunction with conventional somatic cell hybrid panels (Lafreniere et al., 1991; Gorski et al., 1992).

Xq11.1 to Xq23

At least a third of the estimated DNA in this region of the X has been reported in YAC contigs from a number of groups. Contigs of at least 1.0 megabase were reported for the region from DXS135 to the cell cycle gene CCG1 (~2.5-3.0 Mb; Kere et al., 1993; abs. 21; abs. 39, abs. 40, abs. 46), from the ribosomal protein gene S4 (RPS4X) to DXS128E (2.6 Mb; abs. 85), from DXS441 to DXS356 (abs. 29), from DXS56 to the phosphoglycerate kinase gene (PGK1)(1.0 Mb; Turner et al., 1992; abs. 46; abs. 29), from DXS118 to DXS122 (1.3 Mb, abs. 72), from DXS366 to DXS87 (7.5 Mb; abs. 6), and around the collagen gene COL4A5 (1.6 Mb; Vetrie et al., 1992; abs. 72). In addition, a number of YACs for individual loci have been isolated and are indicated in figure 3. In some cases, the YAC contigs have been confirmed by extensive restriction mapping of the YACs (abs. 6, abs. 29, abs. 85), of the genome (Lafreniere and Willard, 1993; Vetrie et al., 1993; O'Reilly et al., 1993), or both. In most cases, YACs were identified by STS screening; the density of STS's in some of the extensive contigs is approaching 1 per 100 kb.

A number of highly informative microsatellite loci have been well-localized on the consensus map and/or in contigs and thus provide integrated tools for disease gene mapping by linkage. DXS981 (Mahtani and Willard, 1993) is tightly linked to DXS159 and DXS467, distal to AR and PGKP1, but proximal to DXS106, and maps physically to the same interval as these markers in Xq12. DXS453 (which detects the same polymorphism as DXS983; abs. 46) maps physically within the DXS135 to DXS348 contig, distal to the ectodermal dysplasia translocation breakpoints, and has been mapped genetically by Huang et al. (1992). New microsatellite polymorphisms have been described for DXS106 and DXS227 (Fairweather et al., 1993), both of which are finely localized within contigs (abs. 46, abs. 40, abs. 85). DXS1105 has been mapped physically to the COL4A5 contig in Xq23 (abs. 72).

Kere et al. (1993; abs. 39) and Chelly et al. (abs. 46) reported extensive YAC contigs that span translocation breakpoints in ectodermal dysplasia that have been previously mapped by several groups (abs. 93; Zonana et al., 1993; Plougastel et al., 1992). This localization is consistent with genetic mapping of the EDA gene between the phosphoglycerate kinase pseudogene (PGKP1) and DXS453 in Xq12-q13.1 (Zonana et al., 1992). Kere et al. have cloned one of the translocation breakpoints and have isolated a candidate cDNA that spans two breakpoints (abs. 39). Experiments to confirm that this corresponds to the EDA locus are underway.

Lafreniere et al. (abs. 85) reported a contig of the X inactivation center (XIC) region, including the XIST gene. The candidate XIC region, defined by patient breakpoints on structurally abnormal inactive X chromosomes, consists of ~800-1200 kb within the 2.6 Mb contig. XIST is the only identified gene within the XIC region. The order of loci in this region (cen - CCG1-RPS4X - PHKA1 - XIST - PGK1 - qter) is identical to that reported in a YAC contig of the comparable region of the mouse X chromosome (abs. 2). Avner presented genetic data to suggest that the mouse Xce and Xist loci were not identical, even though closely linked (abs. 2). Thus, the demonstrated effect of the Xce locus on X inactivation may involve a gene separate from (but conceivably working in concert with) the Xist gene.

Turner et al. (1992) reported a 1.0 Mb YAC contig that spanned the Menkes syndrome translocation breakpoint proximal to PGK1. Three groups subsequently reported isolation and characterization of the Menkes gene (MNK) (Vulpe et al., 1993; Chelly et al. 1993; Mercer et al., 1993). Gecz et al. (abs. 30) reported isolation of three additional genes by cDNA selection within this contig proximal to MNK. One of these encodes a presumptive nuclear protein.

Bentley and colleagues reported an extensive series of experiments to contig much of Xq22 (Bentley et al., abs. 6). The 7.5 Mb contig includes the genes for agammaglobulinemia (AGMX1), alpha-galactosidase (GLA), and proteolipid protein (PLP). Refined physical mapping in the region (O'Reilly et al., 1992, 1993; Parolini et al., 1993; Vetrie et al., 1993) and genetic localization of AGMX1 (Lovering et al., 1993; Parolini et al., 1993) led to isolation of that gene near DXS178 and GLA by direct cDNA selection using a YAC from the region and a Burkitt's lymphoma cDNA library (Vetrie et al., 1993; abs. 81). The gene enclodes a src-like protein-tyrosine kinase and has been called ATK (agammaglobulinemia tyrosine kinase). Point mutations discovered in several patients constitute the strongest proof implicating this gene in AGMX1 (Vetrie et al., 1993). The same gene was independently cloned by Tsukada et al. (1993) by searching for B cell-specific genes mapping to Xq22.

Refined genetic mapping of the X-linked severe combined immune deficiency gene (SCIDX1) by de Saint Basile and colleagues localized the gene between DXS135 and DXS227 in Xq12-q13.1 (Markiewicz et al., 1993). The gene responsible for SCIDX1 has now been shown to be that for the interleukin-2 receptor gamma chain (IL2RG) (Noguchi et al., 1993; abs. 94). The gene was isolated and shown to map to Xq13, and mutations were detected in SCIDX1 patients (Noguchi et al., 1993). Puck et al. (abs. 94) further localized the IL2RG gene to Xq13.1 in the same interval as CCG1 and connexin 32 (GJB1), consistent with the genetic data, and demonstated mRNA-deficiency and point mutations in several patients. Further mapping in this interval (interval 8 of Lafreniere et al., 1991) has been reported in radiation hybrids (abs. 69) and using an X;13 translocation observed in a female patient with mental retardation (abs. 21). Both studies demonstrate that GJB1 maps proximal to CCG1 and support the order cen - DXS348 -GJB1 - t(X;13) - CCG1 - DXS131 qter. It will be important to map the IL2RG gene with respect to this translocation. Cremers and colleagues (abs. 21) have isolated a YAC and cosmid contig that spans the t(X;13) breakpoint and have isolated a candidate cDNA that is currently under study.

Philippe et al. (abs. 22) reported refinement of the physical map in Xq21, using a panel of deletion and translocation breakpoints. Forty DNA markers were assigned to 20 intervals, providing an excellent framework that should be of value for YAC contig assembly in this region. The order of these markers is incorporated into figure 3.

Improved localization has been reported for a number of X-linked genes mapping to this region. Juberg-Marsidi syndrome, a rare X-linked recessive condition characterized by severe mental retardation, growth failure, deafness, and microgenitalism, has been mapped to Xq12-q21, between DXS159 and DXYS1X (Saugier-Veber et al., 1993). An X-linked cleft palate gene (CPX) has been mapped in a British Columbia kindred to Xq13-q21 between PGK1 and DXYS1X (S. Gorski et al., 1992) and in an Icelandic pedigree between DXS326/DXS349 and DXYS1X (abs. 73). Thus, it is likely that the same gene is involved in both families. The dystonia-parkinsonism syndrome gene (DYT3) was mapped to the region between PGK1 and DXS159 (Graeber et al., 1992). Since these flanking markers lie within a 1.0 Mb YAC contig (see above), positional cloning of the gene should now be possible. Higgs and colleagues reported localization of X-linked alpha thalessemia and mental retardation (ATRX) to Xq12-21.31, between DXS106 and DXYS1X (Gibbons et al., 1992). X-linked Charcot-Marie-Tooth Disease (CMTX) has been mapped to Xq11.2 to Xq21.1, between PGKP1 and DXS72, with complete linkage to PGK1 and DXS453 (Bergoffen et al., 1993). The DFN3 deafness gene has been finely mapped in Xq21.1 between DXS26 and DXS121 (Bach et al., 1992; abs. 22).

Finally, two new genes were described. Schwartz et al. (abs. 70) reported linkage data in two families with Renpenning Syndrome (severe mental retardation). The data suggest localization between Xp11.2 and Xq12. Zonana et al. (abs. 88) reported a new entity involving both ectodermal dysplasia and immunodeficiency (with hyper-IgM) in two families with apparent X-linked inheritance. Discordancy between affected siblings excluded both the EDA and Hyper-IgM (CD40L in Xq26) regions of the X, suggesting that the disorder does not involve either (or both) of these previously described loci. Additional mapping studies are required to localize the gene definitively in these families.

Xq24-Xqter

YAC-based contigs assembled and analyzed by their content of STS content, hybridization probes, and fingerprinting methods now essentially cover the region.

The longest set of unambiguously ordered and oriented contigs have been assembled across about 30 Mb of YAC contigs in Xq26-qter. Part of Xq26 has also been assembled by independent methods (Cole et al., 1992). Contigs are now further rationalized by fingerprinting analyses (abs. 57) and by the contents in the YACs of 130 STSs and 400 hybridization probes (abs. 56, 67, and 24). Localized regions have been further fitted with cosmids, in 80 contigs across much of Xq28 (abs. 41), and also across regions both centromeric and telomeric of the color vision loci (GCP/RCP) (abs. 41, abs. 78).

Large stretches of Xq26-qter have now been further studied at 50-300 kb resolution for their overall base content of GC (abs. 56), for the presence of rare-cutter restriction sites and CpG islands (abs. 24, 56, 41, and 78), and for the distribution of Alu and L1 repetitive elements (abs. 57). No strict correlation of any sharp changes in these parameters with likely borders of the cytogenetic bands or subbands defined by classical staining methods has been seen. Alu and L1 elements showed clustering only at a scale of resolution lower than 100 kb, for example in 500 YACs distributed across all of Xq24-qter. GC content, however, did show generally higher levels in q26 and q28 compared to q27, as expected for G vs. R bands; and consistent with Bernardi's earlier analyses (Bernardi, 1989) large regions of "isochores" of relatively constant GC level were observed across megabase regions. In the 13 of the 30 Mb of Xq26 and Xq28 studied thus far, there was a correlation of GC level with CpG island content. The highest GC levels observed correlated with the subtelomeric region around GCP/RCP that contains up to 1 CpG island per 30-50 kb (#'s 24, 41, 78).

Systematic functional mapping is being pursued based on CpG island studies and direct selection by several groups. Tsuji et al. reported on 11 expressed sequence tagged sites (ESTs) in Xq24-qter (abs. 79), 10 of them now localized within YAC contigs; and the laboratories of Poustka (abs. 41) and Toniolo (abs. 78) reported on a number of cDNA clones, one set (abs. 41) across Xq27.3-qter, the other (abs. 78) for the concentrated region of CpG islands (see also Tribioli et al., 1992; Maestrini et al., 1992a and b) around the GCP/RCP cluster. At least nine genes have been localized in 300 kb of the color vision-G6PD region, and 10 in about 1 Mb of the L1CAM-color vision region.

As in Xq26-qter, the 20 Mb region of Xq24-q26.1 has also been assembled in 13 YAC contigs that sum to about 19 Mb and have an average size greater than 1 Mb (abs. 54). Currently 12 contigs have been further rationalized and 10 have been at least partially ordered using hybrid panels (abs. 27), the order of linkage markers, and FISH. Additional YAC contigs have been assembled in the characterization of the region containing the X-linked lymphoproliferative disease gene (XLP) (abs. 75 and Wang et al., 1993).

Many disease gene hunts have progressed considerably. Studies of deletion patients provided more precise localizations for X-linked lymphoproliferative disease in Xq25, close to DXS739 (LYP, abs. 75; Skare et al., 1993), and for myotubular myopathy (MTM1, abs. 44). Much of the Xq25 region seems devoid of indispensible genes, since patients with cytogenetically detectable deletions that remove about two-thirds of the band (including DXS6, DXS100, and DXS739) have no phenotype other than LYP (Skare et al., 1993). A gene for split-hand/split-foot anomaly (OMIM 313350) segregating in a large family was mapped to Xq25-q26, between DXS424 and DXS102 (z=5.13 and 4.43 at theta=0 for DXS294 and HPRT< respectively (ul Haque et al., 1993). Localization of the Borjeson-Forssman-Lehman syndrome (BFLS) to Xq26-q27.1 was confirmed by study of additional families and markers (z=6.07 at theta=0 for DXS144E, abs. 53). A variant form of amelogenesis imperfecta (AIH3) also showed linkage to DXS144E (multipoint lod score of 2.84 at theta=0; Aldred et al., 1992a). Linkage analysis in a family with infantile X-linked cardiomyopathy was consistent with localization in Xq28 (abs. 50), and this disease might be a more severe allelic form of Barth syndrome (endocardial fibroelastosis, EFE2).

Other searches, abetted by the availability of a number of YAC and cosmid resources and maps, have newly arrived at the stage of identification of the genes. Most notable are the published findings of X-linked hypergammaglobulinemia in Xq26 (Allen et al., 1993; Aruffo et al., 1993; di Santo et al., 1993; Korthauer et al., 1993); the association of the L1CAM gene in Xq28 with hydrocephalus [abs. 38, adding data on several mutational changes to the original report of Rosenthal et al., 1992], and adrenoleukodystrophy (ALD) in Xq28 (reviewed with additional information about both ALD and nearby transcripts in abs. 89). Further studies of known disease genes included the analysis of changes in the DNA of a series of IDS patients (abs. 74), analysis of the dbl oncogene (abs. 25) and complete

sequencing of 35 kb containing the FMR1 gene (abs. 55) and 15 kb containing the L1CAM gene (abs. 61). Also in the gene-rich region of distal Xq28 are the genes for congenital nephrogenic diabetes insipidus [the report of Seibold et al. (1992) is added to those in CCM92] and the putative location for Emery-Dreifuss muscular dystrophy (Wehnert et al., 1991; Kress et al., 1992; Cole et al., 1992; Yates et al., 1993). The linkage between manic depression and X-chromosome markers has, however, become weaker (Baron et al., 1993). For incontinentia pigmenti (IP), three Finnish families showed recombination with the loci in both Xq28 and Xp11 (Nyden-Granskog et al., 1993), suggesting the possibility of yet a third IP locus.

Analysis of the Fragile X region has continued with a variety of structural and functional studies, including an examination of possible effects of substantial deletions in the region of the FMR1 and IDS genes on X-inactivation (abs. 44, 68), and description of the FMR1 gene structure (abs. 55). A new fragile site (FRAXF) with apparently reduced folate sensitivity was identified in one family, with the order determined by FISH analysis as FRAXA-DXS465-FRAXE-DXS296-DXS479-IDS, FRAXF-DXS305/374 (Hirst et al., 1993).

Concerning the more general functional analysis of the region, in addition to the identification of large numbers of transcripts and CpG islands that are mentioned above (abs. 24, 42, 56, 78, and 79), a number of additional specific gene assignments were made. They included the finding in Xq24-q27 of a pseudogene of glycerol kinase (abs. 66); in Xq26, of a zinc finger protein gene (abs. 82; see also Villa et al., 1992); and in Xq28, of the renin-binding protein gene (abs. 80) and a zinc finger gene of the Kruppel type (#34). In addition, the biglycan gene (BGN), which had been localized to Xq28, was excluded as a candidate gene underlying the Happle syndrome in man (Traupe et al., 1993), as it had been for the homologous "bare patches" mutation in the mouse (Chatterjee et al., 1993).

A processed pseudogene of B-raf type (Eychene et al., 1992) and a glutamate receptor gene (Gregor et al., 1993), were mapped to Xq24-q25, and a serotonin receptor 1c gene has been assigned to q24 (Milatovich et al., 1992).

Gibbs et al. (abs. 32) reported on sequence analyses of the mouse Xist gene and an anonymous Xq28 cosmid, as well as FMR1, by large-scale shotgun methods; and in the other most extensive sequencing initiative thus far, Chen et al. (abs. 15) have analyzed the sequence of 53 kb extending toward the centromere from the G6PD gene.

Conclusions

The rapid progress in physical, cytogenetic, and genetic mapping has accelerated the synergistic development of an integrated map: genetic markers, hybrid breakpoints, deletions in patient DNAs, and other independently determined features anchor the YAC contigs, while the contigs localize and define the DNA distances that correspond to recombination distances. The major paradigm for disease gene searches remains positional cloning, now often aided by the recovery of a candidate region recovered in YACs (for example, in th finding of the gene for X-linked agammaglobulinemia by Vetrie et al. (1993).

Especially notable at XCW4 was the increasing impact of functional analysis based on the genome map -- both for systematic recovery of genes in a region by modifications of direct selection, and for the interpretation of gene content from sequence data. As expected, the syntenic equivalence of gene content and order in human and mouse is also aiding in the analysis of both genomes. Many similarities were reported in the regions of the Menkes gene (abs. 8), the X inactivation center (abs. 2, abs. 85), segments of Xp11.2 (abs. 9), X-linked hypophosphatemia (abs. 76), and Xq28 (abs. 36). As YAC contig assembly in the mouse proceeds (abs. 11), future XCW's can expect to see comparative mapping meld with comparative sequencing to provide an idea of the course of evolution of mammalian genomes.

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[Note:References of the type "abs. 34" are not listed here, but refer to the numbered abstracts from the meeting, contained as part of this report.]

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DISCLAIMER

Table 1. X Chromosome Genes in pter-qter Order, with references

CSF2RA	GDB
IL3RA	Abs. 92
XE7	Abs. 26
ASMT	Abs. 92
ANT3	GDB
MIC2	GDB
GS1	Yen et al. 1992
STS	GDB
KAL	GDB
AMELX	GDB
PRPS2	GDB
GLRA2	GDB
XE59	Ellison et al. 1992a
PDHA1	GDB
GRPR	Abs. 10
SSAT	Xiao et al. 1992
PHKA2	Hendrickx et al. 1993
HSMXS	Reik et al. 1992
ZFX	GDB
POLA	GDB
GK	GDB
DMD	GDB
CYBB	GDB
OTC	GDB
MAOA	GDB
MAOB	GDB
NDP	GDB
UBE1	GDB
ARAF1	GDB
SYN1	GDB
TIMP1	GDB
PFC	GDB
ELK1	Abs. 42
ZNF21	GDB: Abs. 42
ZNF81	Abs. 42
OATL1	GDB
GATA1	GDB
SYP	GDB
TFE3	GDB
OATL2	Abs. 84
ALAS2	GDB
MTHFDL1	GDB
ZXDB	Greig et al. 1992
ZXDA	Greig et al. 1992
AR	GDB
GJB1	GDB
IL2RG	GDB
CCG1	GDB
RPS4X	GDB
PHKA1	GDB
XIST	GDB
MNK	GDB
PGK1	GDB
ZNF6	GDB
CHM	GDB
AGMX1	GDB
GLA	GDB
PLP	GDB
COL4A5	GDB
LAMP2	GDB
UBE2A	GDB
SNF2L	GDB
OCRL	GDB
HIGM1	GDB
ZNF75	Villa et al. 1992 Abs. 82
HPRT	GDB
F9	GDB
MCF2	GDB
CDR1	GDB
FMR1	GDB
TH4	Abs. 79
IDS	GDB
RENBP	GDB: Abs. 80
TH27	Abs. 79
GABRA3	GDB
HZF22	Abs. 34
ALD	GDB
"CDM"	Abs. 89
BGN	GDB
L1CAM	GDB
AVPR2	GDB
RCP/GCP	GDB
G6PD	GDB
MPP1	GDB
F8C	GDB
AMD2	GDB: Xq22-q28
MYCL2	GDB: Xq22-q28
PRPS1	GDB: Xq21-q27
TBG	GDB: Xq21-q22
ANT2	GDB: Xq13-q26
CHR39C	GDB: Xq13-q26
CALB3	GDB: Xp
PFKFB1	GDB: X

Legend

Genes described for the human X chromosome are listed in approximate order from pter to qter as shown on the map in Figure 1. References are provided for those genes not yet listed in the Genome Data Base as well as a few of the new identifications or localizations.

Table 2. X Chromosome Breakpoints

Breakpoint Number (Figure 1)	Name of Cell line, GDB breakpoint number, or type of disorder if a patient	Reference
1	PORCH9	Slim et al 1993 Genomics in press
2	KICH6	Slim et al 1993 Genomics in press
3	BXP8 BXP9 BXP12 BXP10	GDB, Schaefer et al 1993 Nature Genet in press
4	BXP18 BXP14	GDB, Schaefer et al 1993 Nature Genet in press
5	BXP20 BXP22 BXP24 BXP28 BXP26 BXP30	GDB, Schaefer et al 1993 Nature Genet in press
6	BXP32 (STS)	GDB, Schaefer et al 1993 Nature Genet in press
7	BXP33	GDB, Schaefer et al 1993 Nature Genet in press
8	BXP34 BXP21	GDB, Schaefer et al 1993 Nature Genet in press
9	BXP23 BXP25	GDB, Schaefer et al 1993 Nature Genet in press
10	BXP35	GDB, Schaefer et al 1993 Nature Genet in press
11	BXP29 BXP19 BXP37 BXP36	GDB, Schaefer et al 1993 Nature Genet in press
12	BXP38	GDB, Schaefer et al 1993 Nature Genet in press
13	BXP39 BXP40 BXP41 BXP42	GDB, Schaefer et al 1993 Nature Genet in press
14	BXP73 (KAL)	GDB, Schaefer et al 1993 Nature Genet in press
15	BXP27 BXP31	GDB, Schaefer et al 1993 Nature Genet in press
16	BXP43	GDB, Schaefer et al 1993 Nature Genet in press
17	BXP13	GDB, Schaefer et al 1993 Nature Genet in press
18	BXP44 BXP11	GDB, Schaefer et al 1993 Nature Genet in press
19	BXP45	GDB, Schaefer et al 1993 Nature Genet in press

Breakpoint Number (Figure 1)	Name of Cell line, GDB breakpoint number, or type of disorder if a patient	Reference
20	BXP72 BXP15	GDB, Schaefer et al 1993 Nature Genet in press
21	BXP46	GDB, Schaefer et al 1993 Nature Genet in press
22	BXP47	GDB, Schaefer et al 1993 Nature Genet in press
23	BXP49 BXP48	GDB, Schaefer et al 1993 Nature Genet in press
24	BXP50	GDB, Schaefer et al 1993 Nature Genet in press
25	BXP51 BXP52 BXP53	GDB, Schaefer et al 1993 Nature Genet in press
26	BXP54 BXP55	GDB, Schaefer et al 1993 Nature Genet in press
27	BXP56	GDB, Schaefer et al 1993 Nature Genet in press
28	BXP58 BXP57	GDB, Schaefer et al 1993 Nature Genet in press
29	BXP60 BXP59	GDB, Schaefer et al 1993 Nature Genet in press
30	BXP70 (AHC/GK) BXP71 (AHC/GK)	GDB, Schaefer et al 1993 Nature Genet in press, Worley et al 1993 Genomics 16:407.
31	DXS669, J-Oregon AHC/GK/DMD deletion breakpoint	Pillers et al Hum. Genet 47:7951
32	Rett's syndrome (RTT) translocation breakpoint;	Zoghbi et al. 1990 Am J Med Genet.35:148.
33	DXS708, JC-1 deletion breakpoint (GK)	Love et al 1990 Genomics 8:106.
34	DXS268, J-66 deletion breakpoint (DMD)	Van Ommen et al.1987 Genomics 1:329.
35	DXS269, P20 deletion hotspot (DMD)	Blonden et al 1989 Nucleic Acids Res.17:5611.
36	DXS270, J-BIR deletion breakpoint (DMD)	Monaco et al 1987Hum. Genet.75:221
37	DXS271, SKI deletion breakpoint (DMD)	Forrest et al 1987 Cytogenet Cell Genet 46:615.
38	DXS164, many deletion breakpoints (DMD)	Monaco et al., 1987 Hum. Genet 75:221
39	DXS206, XJ t(X;21) (DMD) translocation breakpoint	Ray et al 1985 Nature 318:672
40	DXS272, J-47 deletion breakpoint (DMD)	Monaco et al 1987 Hum Genet. 75:221
41	DXS709, J-JD deletion breakpoint (DMD)	Ho et al 1992 Am J. Hum. Genet.50:317

Breakpoint Number (Figure 1)	Name of Cell line, GDB breakpoint number, or type of disorder if a patient	Reference
42	DXS1082, J-BB deletion breakpoint	Musarella et al 1991 Genomics 11:263
42.5	TG5SC.1	Bergen et al 1993 Cytogenet. Cell Genet. 62:231
43	Finnish NDP deletion	de la Chapelle et al 1985 Clin. Genet. 28:317
43.5	B.T. NDP deletion	Diergaarde et al 1989 Hum. Genet. 84:22
44	t75-2ma-1b	Lafreniere et al Genomics 1991,11:352
45	Synovial sarcoma translocation t(X;18)	de Leeuw et al 1993 Genes, Chromosomes & Cancer 6:182-189.
46	SIN 176	Lafreniere et al 1991 Genomics 11:352
47	DUAIA	Lafreniere et al 1991 Genomics 11:352
48	Synovial sarcoma translocation	Knight et al Hum. Mol. Genet. 1992 1:633-637
49	A62-1A-4b L62-3A 88H5	Lafreniere et al 1991 Genomics 11:352
50	FGDY translocation t(X:8)	Rafael et al 1992 Amer. J. Hum. Genet. 51:A116, Abs. 33
51	IP1 t(X;13) and t(X;9) translocations	Gorski et al 1992 Genomics 14:649-656 Gorski et al 1992 Genomics 14:657-665
52	IP1 t(X;17) translocation	Gorski et al 1992 Genomics 14:649-656 Gorski et al 1992 Genomics 14:657-665
52.5	A48-1Fa	Lafreniere et al 1991 Genomics 11:352
53	A63-1A	Lafreniere et al 1991 Genomics 11:352
54	t60PP-6A	Brown et al 1989 Cytogenet. Cell Genet. 51:970
55	KM	Cremers et al. 1988 Amer J Hum Genet 43:452
56	t11PP-4A	Brown et al 1989 Cytogenet. Cell Genet. 51:970
57	t60PP-29A-1a (p)	Brown et al 1989 Cytogenet. Cell Genet. 51:970
58	AK (EDA)	Kere et al 1993 Genomics 16:305
58.5	AnLy (EDA)	Shows and Brown 1975 Proc Natl Acad Sci USA 72:2125
59	t11PP-6A	Lafreniere et al 1991 Genomics 11:352
60	t(X;13)	Abs. 21
61	A68-2A	Lafreniere et al 1991 Genomics 11:352
62	t11PP-5A	Lafreniere et al 1991 Genomics 11:352
63	t60PP-29A-1a (d)	Brown et al 1989 Cytogenet. Cell Genet. 51:970
64	t4-1a-az1 W4-1A	Lafreniere et al 1991 Genomics 11:352
65	t60PP-25A	Brown et al 1989 Cytogenet. Cell Genet. 51:970
66	tAG-1Baz1b	Lafreniere et al 1991 Genomics 11:352

67	BXP3 (MNK)	GDB; Verga et al. 1991 Amer J Hum Genet 48:1133
Breakpoint Number (Figure 1)	Name of Cell line, GDB breakpoint number, or type of disorder if a patient	Reference
68	t81az1b TEL26	Lafreniere et al 1991 Genomics 11:352
69	XL62-02	Lafreniere et al 1991 Genomics 11:352
70	Ben 3B	Lafreniere et al 1991 Genomics 11:352
71	MBU	Abs. 22
72	7.6 (p) 25.6 (p)	Abs. 22
73	TDo (CHM)	Abs. 22
74	A50-1AcL3A	Lafreniere et al 1991 Genomics 11:352
75	LGL2905 (d)	Abs. 22
76	FA	Abs. 22
77	BC	Abs. 22
78	X3000-11.1	Nussbaum et al 1986 Am J Med Genet 23:457
79	F649-5 (OCRL)	Attree et al 1992 Nature 358:239
80	LL556 (p)	Suthers et al 1990 Am J Hum Genet 47:187
81	BXP5	GDB, Suthers et al 1990 Am J Hum Genet 47:187
82	BXP6	GDB, Suthers et al 1990 Am J Hum Genet 47:187
83	LL556 (d) TC4.8 (p)	Suthers et al 1990 Am J Hum Genet 47:187 Maestrini et al 1992 Am J Hum Genet 50:156
84	Q1Z (FMR1)	Warren et al 1990 Proc Natl Acad Sci USA 87:3856
85	CY34 (IDS)	Suthers et al 1990 Am J Hum Genet 47:187
86	Y162Aza	Suthers et al 1990 Am J Hum Genet 47:187
87	TC4.9 (p)	Maestrini et al 1992 Am J Hum Genet 50:156
88	TC4.8 (d)	Maestrini et al 1992 Am J Hum Genet 50:156
89	TC4.9 (d)	Maestrini et al 1992 Am J Hum Genet 50:156

Legend

The table lists breakpoints sequentially from pter to qter and is keyed to the numbers in Figure 1. Entries with multiple members indicate multiple breakpoints that are indistiguishable by the current probe data. Where available, BXP numbers from the Genome Data Base have been used, and GDB appears in the reference list along with the primary reference. Otherwise, cell line designations have been given, although in some cases, the phenotype of the patient exhibiting the chromosomal abnormality (or the gene in which the disruption has ocurred) has been used. The symbol (p) indicates proximal, and (d) indicates distal in deletions with breakpoints over a distance. Primary references are given with the exception of breakpoints described in abstracts in this report, which are designated with Abs. followed by the number of the abstract.

Table 3. X-Linked Multiallelic Microsatellites

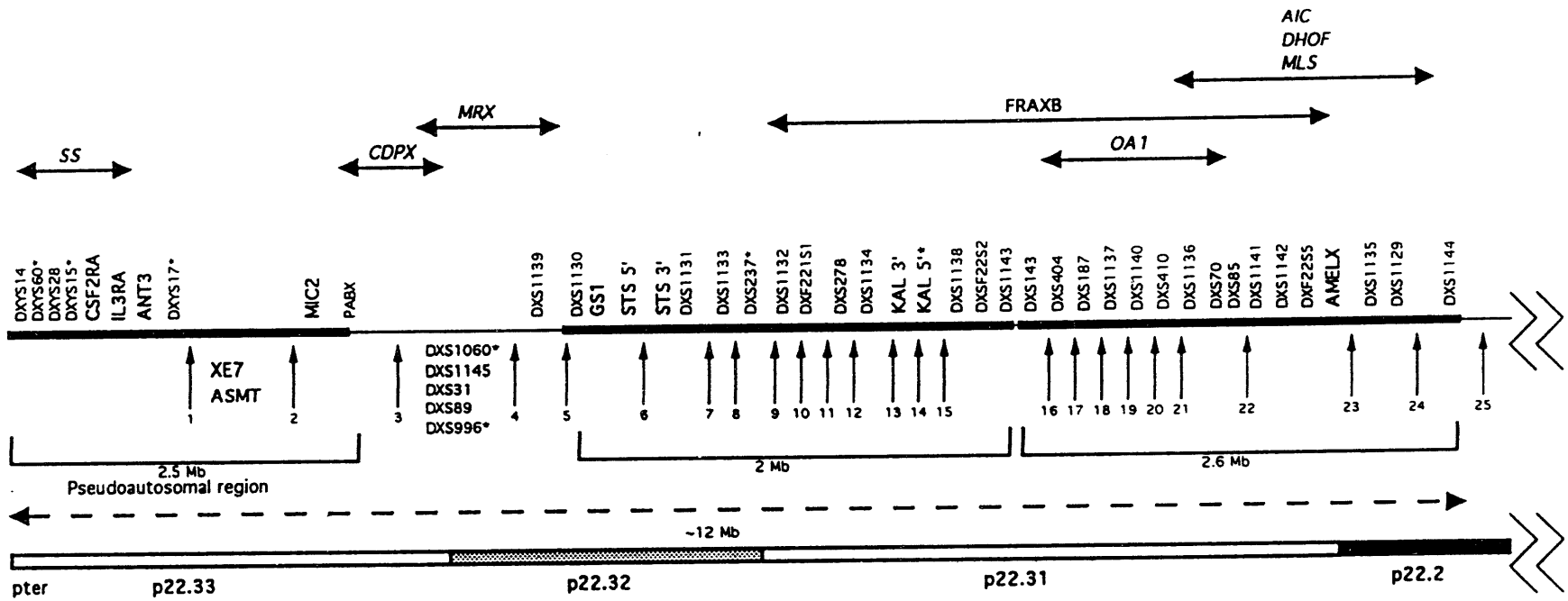
DXS1060, DXS996 (abs.3)
DXS237 (abs.3)
KAL
DXS987 (abs.3; Hanauer, unpublished)
DXS207 (Oudet et al., 1993)
    DXS418 (DXS16-DXS418-DXS999) (abs.23)
    DXS1053 (in same YACs as DXS197, DXS207)(abs.35)
DXS999 (abs.35 and 64)
DXS443 (abs.35 and 64)
DXS365 (abs.35 and 64)
DXS1052 (abs.35 and 64)
DXS274 (abs.35 and 64)
DXS451, DXS989 (abs.3, 40 and 51)
DMD 3' Dys
DMD1c (exon 56-60)
STR50 (Oudet et al., 1992)
STR49 (Oudet et al., 1992)
STR45 (Oudet et al., 1992)
STR44 (Oudet et al., 1992)
    DXS992, DXS985 (DXS989-DXS992,985-DXS164) (abs.49)
    DXS997 (DXS992, 985-DXS997-DXS164) (abs.49)
DMD 5'Dys Muscle promoter (Oudet et al., 1992)
DMD 5'Dys Brain promoter,
    DXS538 (close to DMD 5') (abs.49)
    DXS1068 (DXS164-DXS1068-DXS7) (abs.49 and 52)
DXS1110 (Roux et al., 1993)
"OPC" (<500kb distal to OTC) (abs.28)
    DXS993 (DXS209-DXS993-DXS7) (Abs.4)
    "SP357" (DXS209-"SP357"-DXS7) (Abs.43)
    DXS556 (Xp11.3-p11.23) (Thiselton et al., 1993)
DXS228
DXS7
MAOA
MAOB
AFM 168ya3 (abs.17)
DXS1003 (abs.4 and 17)
SYN1/ARAF1
PFC
DXS426(abs.17)
DXS226 (abs.17)
    DXS1126 (1cM distal to DXS255) (abs.49)
DXS255 (VNTR)

DXS988, DXS1000 (abs.4 and 84)
ALAS2, DXS679 (abs.9)
    DXS991 (DXS988-DXS991-AR) (abs.49, 52 and 84)
AR (Sleddens et al., 1993; abs.49)
PGKP1
DXS981 (Mahtani and Willard, 1993)
    DXS1125 (AR-DXS1125-DXS453) (abs.49)
    DXS1111 (near DXS106,153,159) (Browne et al., 1993)
DXS135 (Markiewicz et al., 1993)
DXS339 (Zonana et al., 1992)
DXS106 (Fairweather et al., 1993)
DXS453/DXS983 (abs.46)
DXS559 (Roustan et al., 1992; Lindsay et al., 1993)
DXS227 (Fairweather et al., 1993)
DXS441/DXS566
DXS56
PGK1
    DXS1124 (DXS1125-DXS1124-DXYS1) (abs.49)
    DXS738 (DXS106-DXS738-DXS3)
    DXS554 (close to PGK1) (Lindsay et al., 1993)
    DXS1002, DXS995 (DXS453-DXS1002, DXS995-DXYS1) (abs.49)
    DXS986 (PGK1-DXS986-DXS26) (abs.18)
    DXS571 (q21.1-q21.3) (Curtis et al., 1992)
DXYS1X
DXS3
DXS990 (abs.49 and 52)
DXS458 (abs.49 and 52)
DXS454 (abs.49 and 52)
DXS178 (de Weers et al., 1992)
DXS265 (Lovering et al., 1993; Parolini et al., 1993)
    DXS1153(DXS454-DXS1153-DXS456) (abs.49)
    DXS1120 (DXS454-DXS1120-DXS456) (abs.49)
DXS456 (abs.49)
DXS1059 (abs.18)
COL4A5 (Farr et al., 1992; abs.72)
DXS1105 (abs.40)
DXS424
    DXS1001 (DXS424-DXS1001-DXS994, DXS1122) (abs.49)
DXS425
    DXS737 (DXS425-DXS737-HPRT) (abs.52)
    DXS994 (DXS425-DXS994-HPRT)
    DXS1122 (DXS425-DXS1122-HPRT) (Abs.49)

DXS692 (DXS100-DXS692-DXS144) (Lasser et al., 1993)
HIGM1/CD40L (near HPRT) (Allen et al., 1993)
DXS1114 (Weber et al., 1993b; abs.67)
HPRT
DXS300 (abs.49 and 67)
DXS1062 (abs.67)
DXS294 (abs.49 and 67)
DXS730 (abs.67)
AFM196xa1 (abs.67)
DXS102
DXS984 (abs.49 and 67)
DXS691 (5cM distal to F9) (Lasser et al., 1993)
DXS292
DXS297
DXS998 (abs.67)
DXS548
FRAXA/FMR1
AFM287ze5 (abs.67)
"UT587" (abs.67; R.White, unpublished)
DXS731 (distal to DXS297)
DXS1123 (1cM distal to FRAXA) (abs.49)
DXS1113 (Weber et al., 1993a), AFM199wc7 (abs.67)
GABRA3
DXS52
F8C
DXS1108 (Freije et al.,1992)
DXYS154 (Freije et al.,1992)

Table 3. X-linked multiallelic microsatellites.

Marker loci are listed from Xp22.3 to q28. Order was derived from genetic maps (Donelly et al, abs.49; Murray et al., abs.52; Weissenbach et al., 1992; NIH-CEPH map [Murray et al., Science 258: 67-86 (1992)], and other regional maps) and from physical maps: YAC contigs, chromosomal breakpoints, telomere breakage (Farr et al., 1992; Bayne et al., abs.18). Markers at the left margin are uniquely ordered, but order may be in some cases based on a single piece of data, and should be considered as tentative. For other markers, flanking loci or other mapping information are indicated. Markers separated by commas are not ordered with respect to one another. Underlined loci are those not listed in the previous compilations (HGM11 and CCM92 reports). Some markers reported at XCW4 or from Genethon (AFM numbers), have no DXS numbers yet. The list includes two minisatellites (DXS255 and DXS52, the latter testable by PCR), but not the minisatellites in the Xp22.3 pseudoautosomal region. Only very recent references and XCW4 abstracts were cited. For other references, see previous reports and GDB.



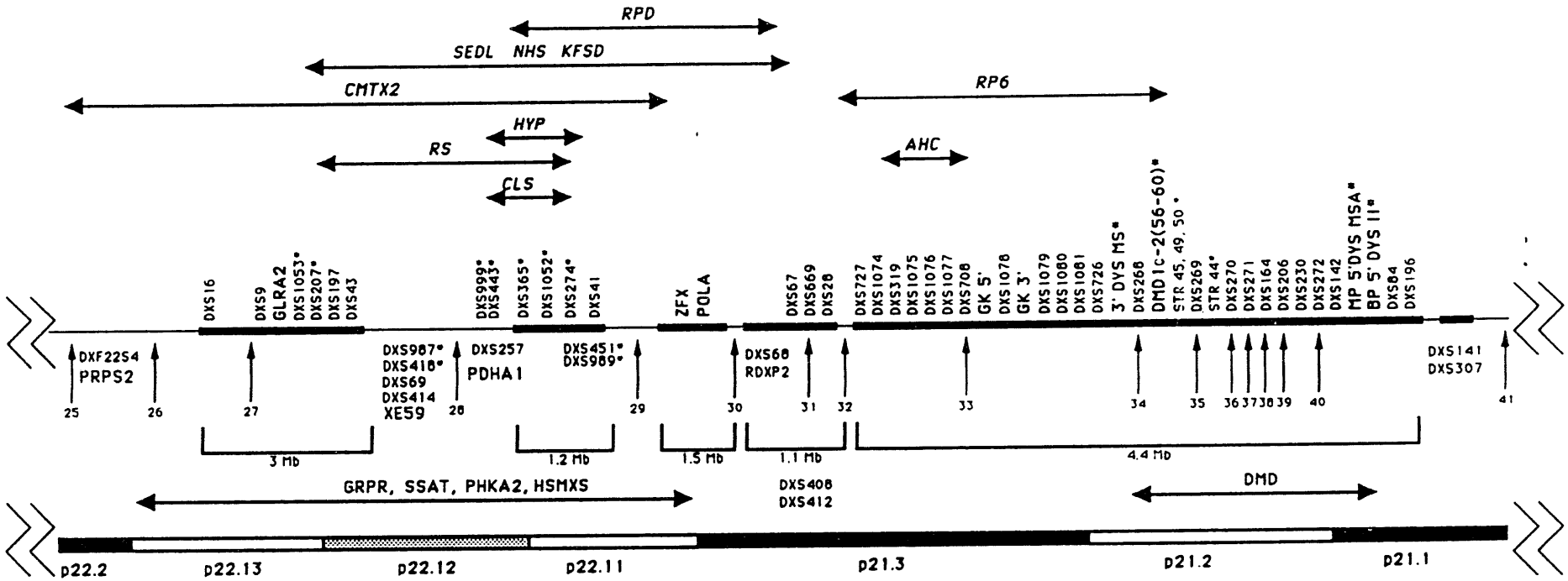
Human X Chromosome

Consensus map

(not to scale)

X ChromosomeWorkshop 4
St. Louis, May 1993

Figure 1



Legend

- Order of markers *above* line is known.
- Expressed genes are in bold type.
- Microsatellite polymorphisms are denoted with an asterisk.
- Markers *below* line are unordered, but are known to map in the interval.

YAC contig

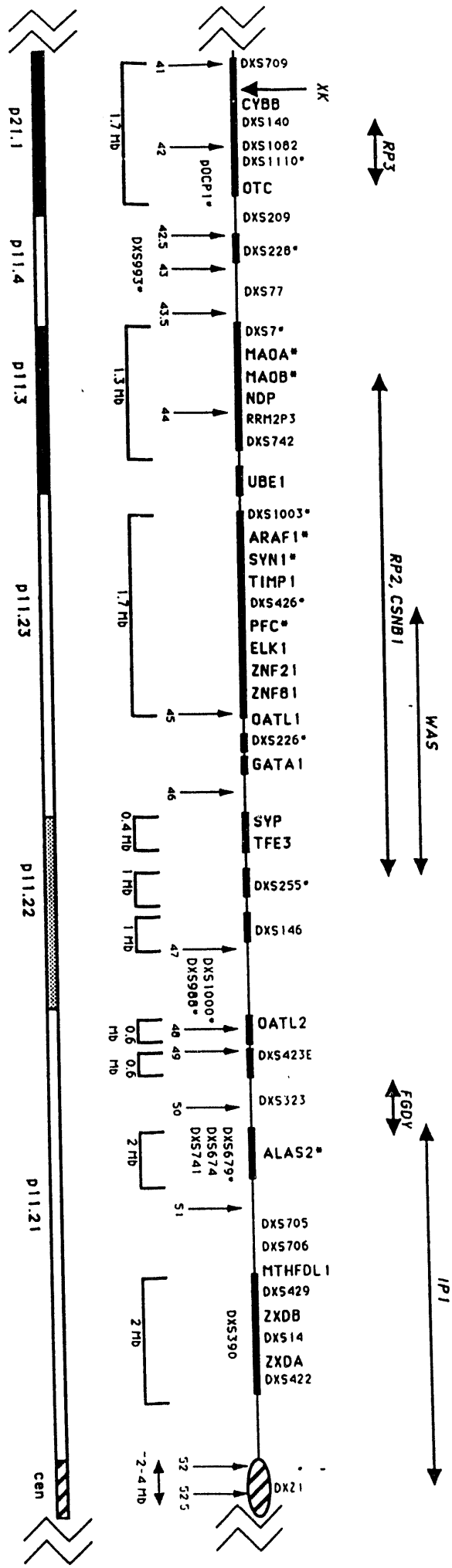
Size of contig

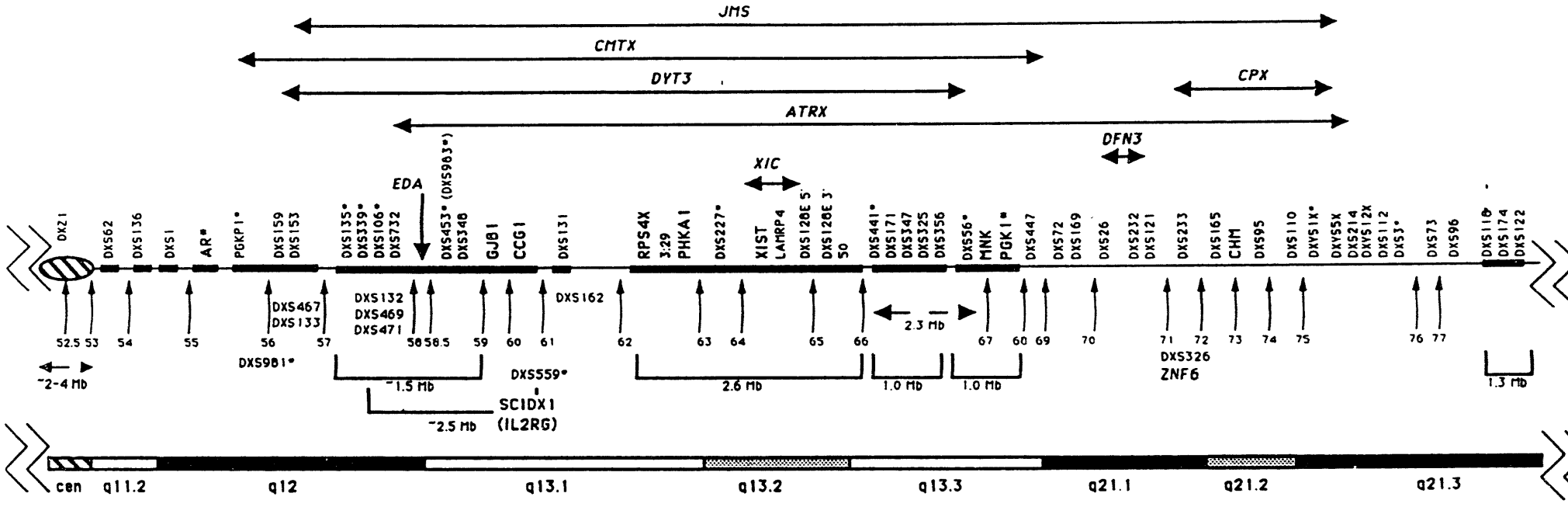
PFGE maps

Gene localization

Breakpoint

52

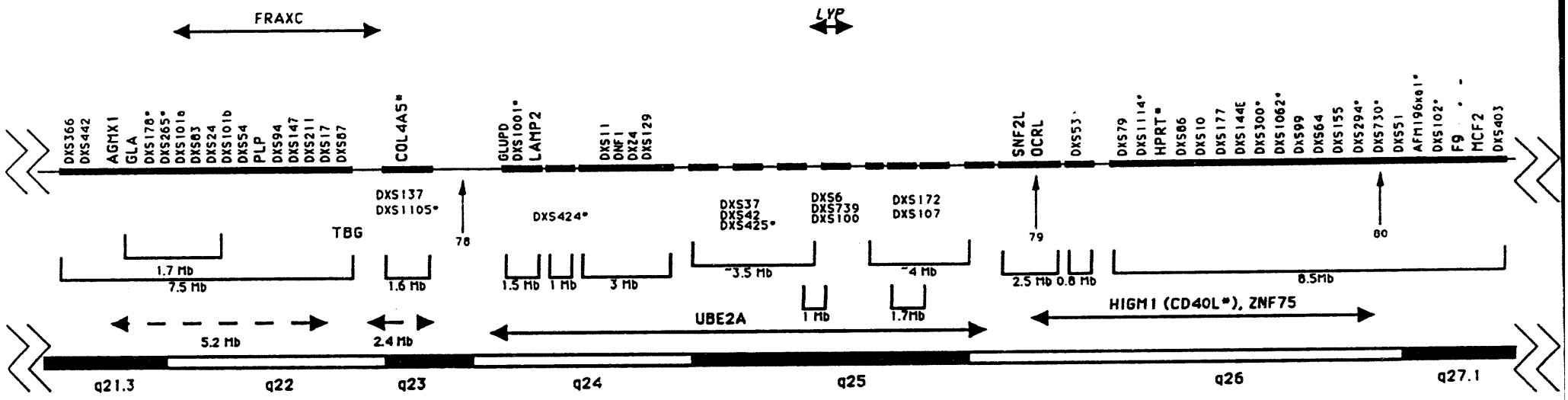

p21.1
p11.4
p11.3
p11.23
p11.22
p11.21
cen
41
42
42.5
43
43.5
44
45
46
47
48
49
50
51
52
52.5
1.7 Mb
1.3 Mb
1.7 Mb
0.4 Mb
1 Mb
1 Mb
0.6 Mb
0.6 Mb
2 Mb
2 Mb
~2-4 Mb
pDCP1*
DXS993*
DXS1000*
DXS988*
DXS679*
DXS674
DXS741
DXS390
DXS709
XK
CYBB
DXS140
DXS1062
DXS1110*
OTC
DXS209
DXS228*
DXS77
DXS7*
MAOA*
MAOB*
NDP
RRM2P3
DXS742
UBE1
DXS1003*
ARAF1*
SYN1*
TIMP1
DXS426*
PFC*
ELK1
ZNF21
ZNF81
OATL1
DXS226*
GATA1
SYP
TFE3
DXS255*
DXS146
OATL2
DXS423E
DXS323
ALAS2*
DXS705
DXS706
MTHFDL1
DXS429
ZXDB
DXS14
ZXDA
DXS422
DXZ1
RP3
RP2, CSNB1
WAS
FGDY
IP1

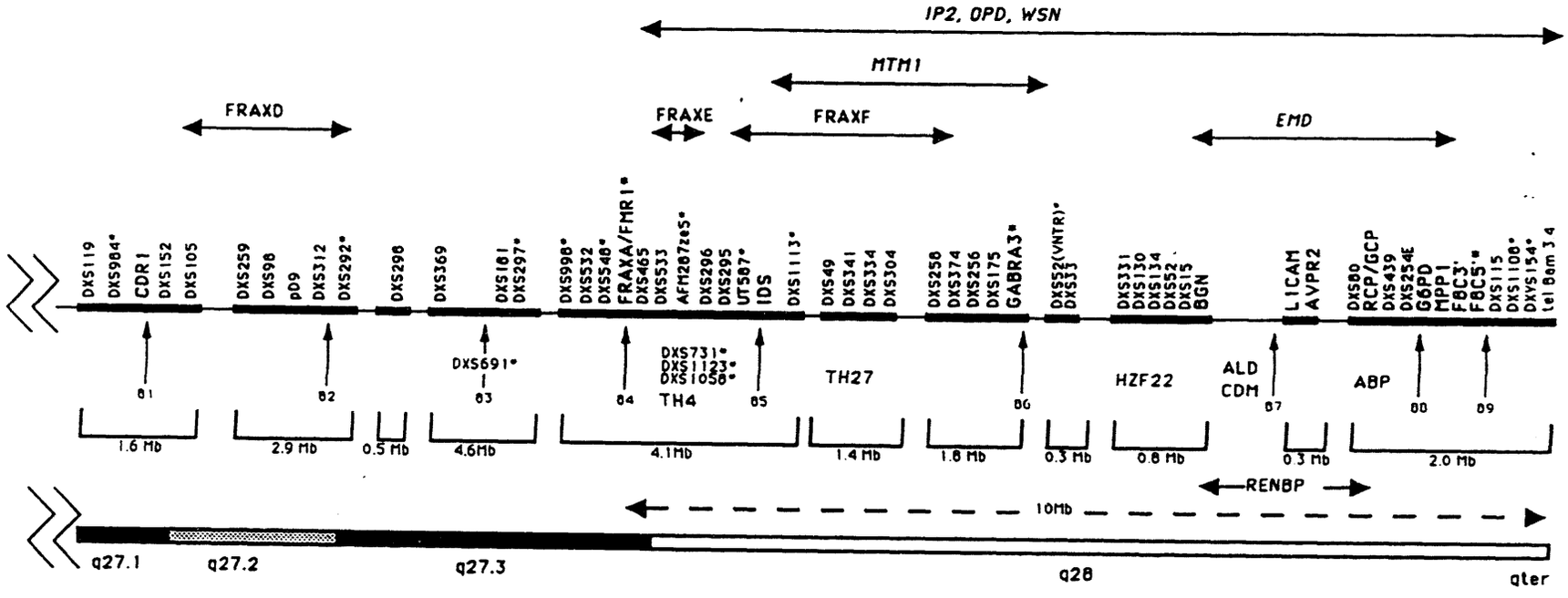


>90 Mb in YAC contigs

85 cloned, expressed and localized genes:
- 44 p arm
- 41 q arm

93 breakpoints:
- 54 p arm
- 38 q arm
- 1 centromere


FRAXC
LYP
DXS366
DXS442
AGMX1
GLA
DXS178*
DXS265*
DXS1016
DXS83
DXS24
DXS1016
DXS54
PLP
DXS94
DXS147
DXS211
DXS17
DXS87
COL4A5*
GLUPD
DXS1001*
LAMP2
DXS11
DNF1
DXZ4
DXS129
SNF2L
OCRL
DXS53
DXS79
DXS1114*
HPRT*
DXS86
DXS10
DXS177
DXS144E
DXS300*
DXS1062*
DXS99
DXS64
DXS155
DXS294*
DXS730*
DXS51
AFM196xe1*
DXS102*
F9
MCF2
DXS403
DXS137
DXS1105*
TBG
76
DXS424*
DXS37
DXS42
DXS425*
DXS6
DXS739
DXS100
DXS172
DXS107
79
80
1.7 Mb
7.5 Mb
1.6 Mb
1.5 Mb
1 Mb
3 Mb
~3.5 Mb
~4 Mb
2.5 Mb
0.8 Mb
8.5Mb
1 Mb
1.7Mb
HIGM1 (CD40L*), ZNF75
UBE2A
5.2 Mb
2.4 Mb
q21.3
q22
q23
q24
q25
q26
q27.1



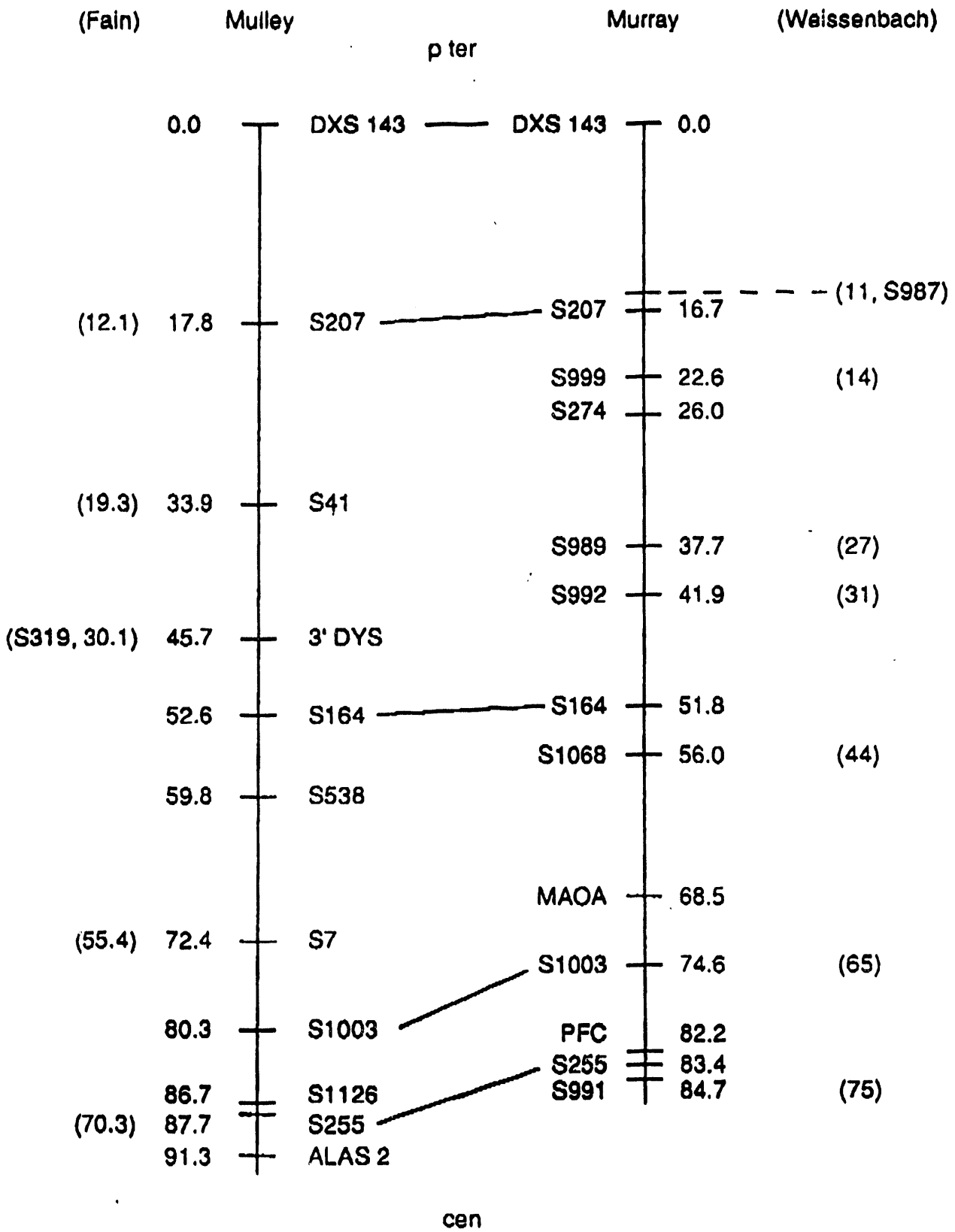
7 Additional cloned genes, less well localized:	
PFKFB1	X
CALB3	Xp
CHR39C	Xq13-q26
ANT2	Xq13-q26
PRPS1	Xq21-q27
MYCL2	Xq22-q28
AMD2	Xq22-q28

Source: Genome Data Base

Fig 2

Genetic maps of the X chromosome

The framework maps presented by Mulley (Donelly et al., abs. 49) and Murray (abs. 52) are aligned, starting at DXS143 in Xp22.3. Genetic map coordinates derived from the map of Fain and Barker (XCW3, in Mandel et al. 1992, CCM92 report) and Weissenbach et al. (1992), are indicated on the left and right respectively, for markers common to the adjacent map (or for a close marker, which is then indicated by its (DX)S number). Coordinates for the Weissenbach map were calculated assuming that DXS143 is 3cM proximal to the DXS1060, which is the most distal Xp marker in that map.


(Fain)
Mulley
Murray
(Weissenbach)
p ter
0.0
DXS 143
DXS 143
0.0
(11, S987)
(12.1)
17.8
S207
S207
16.7
S999
22.6
(14)
S274
26.0
(19.3)
33.9
S41
S989
37.7
(27)
S992
41.9
(31)
(S319, 30.1)
45.7
3' DYS
52.6
S164
S164
51.8
S1068
56.0
(44)
59.8
S538
MAOA
68.5
(55.4)
72.4
S7
S1003
74.6
(65)
80.3
S1003
PFC
82.2
S255
83.4
86.7
S1126
S991
84.7
(75)
(70.3)
87.7
S255
91.3
ALAS 2
cen

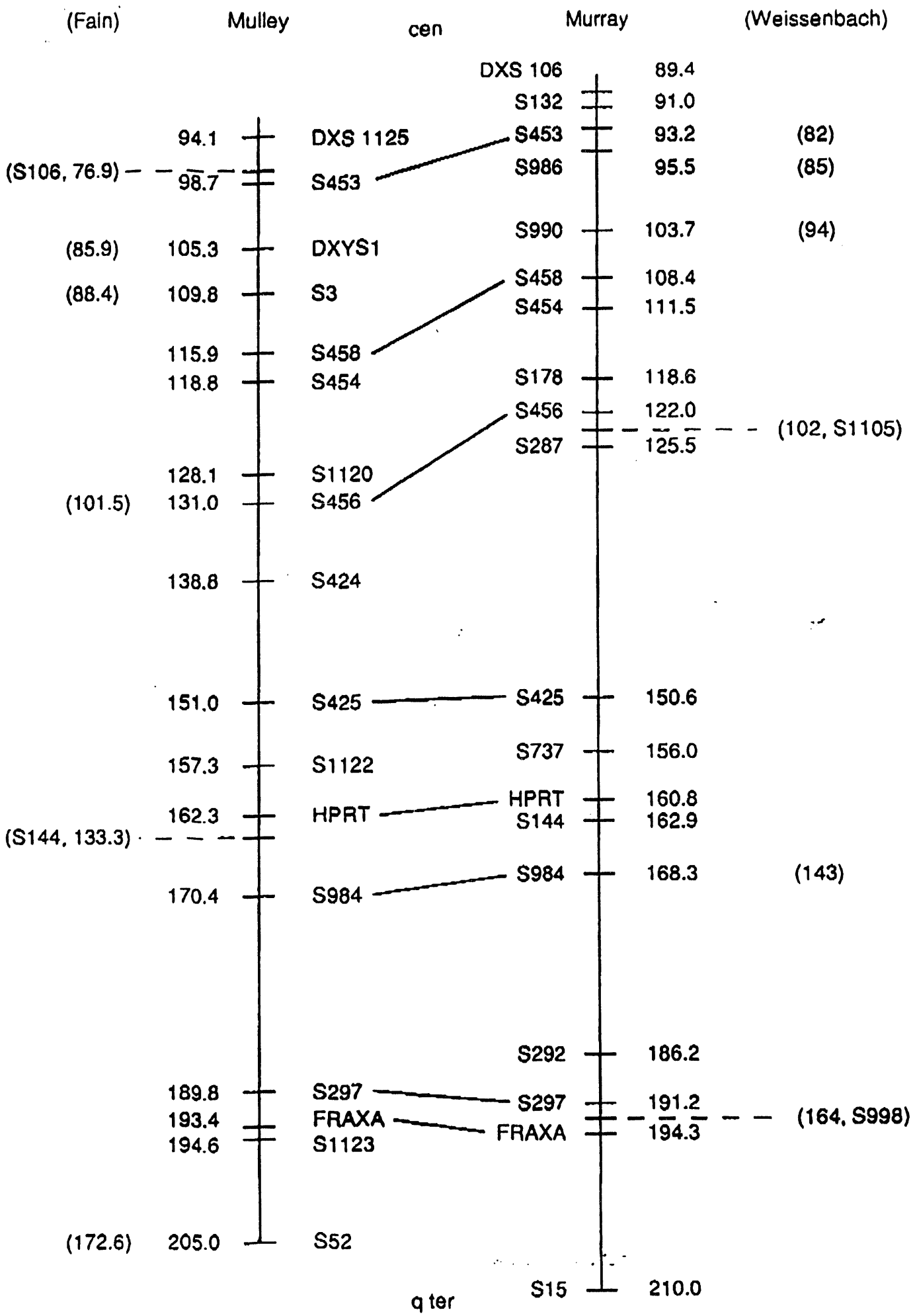


Figure 2. Pg 3 of 3

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