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Report of the fifth international workshop on human X chromosome mapping

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A high-quality integrated genetic and physical map of the X chromosome from telomere to telomere, based primarily on YACs formatted with probes and STSs, is increasingly close to reality. At the Fifth International X Chromosome Workshop, organized by A.M. Poustka and D. Schlessinger in Heidelberg, Germany, April 24-27, 1994, substantial progress was recorded on extension and refinement of the physical map, on the integration of genetic and cytogenetic data, on attempts to use the map to direct gene searches, and on nascent large-scale sequencing efforts.

This report summarizes physical and genetic mapping information presented at the workshop and/or published since the reports of the Fourth International X Chromosome Workshop (XCW4) (Schlessinger et al., 1993) and CCM93 (Willard et al., 1994). The principle aim of the workshop was to derive a consensus map of the chromosome, in terms of physical contigs emphasizing the location of genes and microsatellite markers. The resulting map is presented in figure 1 and updates previous versions (see legend for detailed information on the map and the conventions used in deriving the consensus information). This report also updates the list of highly informative microsatellites, which are marked with asterisks in figures 1 and 2. The text to follow highlights the working state of the map, the genes known to reside on the X, and the progress toward integration of various types of data. The abstracts, on which much of the revised map is based, should be consulted for further information.

Although the degree of map assembly varies from region to region of the chromosome and some small intervals present special problems, concerted efforts are now directed towards the closure phase of mapping for at least 85% of the chromosome, and partial contig coverage of all but the very ends and the centromere is on hand. Workshop discussions thus began to turn increasingly to the resolution of several important outstanding questions. They include the definition of "map closure" and the assessment of the quality of the map, the storage and interchange of information and materials, and the logistics and technology of the next phase of mapping, gene-finding, and sequencing. Such questions affect the entire field of genome studies, but the size of the X chromosome community, the range of its interests, and the intensity of the work on X-linked inherited diseases make this a test case of possible general applicability.

An important result of discussions of the format and quality of maps was the consensus that a number of types of map representation and verification are both necessary and desirable. This is reflected in the consensus map shown in figure 1 and in the text of this report. The need for complex map representation led to discussions of possible movement toward a form of location database. Among the suggestions was the assignment of markers, breakpoints, and other map features along an arbitrary "location" scale that reflects physical distance; the rough "megabase" scale to the left in figure 1 will function as a working model, as initiated at CCM93 (Willard et al., 1994). An alternative suggestion was the definition of marker location in intervals defined by "anchor" points such as the nearest bracketing polymorphic markers.

Issues related to overall physical and genetic mapping and corresponding informatics

In regard to the storage and transfer of materials and information, several groups presented efforts to generate universally available resources. These depended to a considerable extent on the views of what constitutes a finished map ("closure") and which approaches should be used to further the analysis of the chromosome. In general, the tendencies to define a map either as clone-based or as STS marker-based continue in parallel. Therefore, both clones and marker information remain indispensible. Many mapping groups are entering information into local databases and have on hand collections of markers, clones and libraries; but critical reagents are scattered and the burden of distribution is severe.

In attempts to store information, the Genbank and EMBL databases continue to play an essential role in providing general access to sequence information, while the Genome Data Base continues to be the required *locus classicus* for the deposition of physical mapping data and is now accepting STS, YAC and clone identification information, as well as probe/STS content data underlying contig assembly. Regarding map integration and display, several groups have developed analytical and representational tools (abs. 44, 91, and 92). In another approach toward data handling and map assembly and representation, many groups are using the SEGMAP program developed by Green and Magniss (Washington University), while SIGMA (Los Alamos) is providing an interface for the incorporation of SEGMAP output in integrated cumulative maps. Morton (abs. 50) lead a spirited discussion on elements of a location database and described initial efforts to develop such a database for the X chromosome (Wang et al., 1994). Indeed, some of the perceived advantages of such a perspective on map integration are incorporated into the consensus view of the X chromosome map presented in figure 1.

As for the availability of materials, those who define a map in traditional genetic terms as a sequence of ordered markers, with distances defined as precisely as possible, can increasingly depend on the easily-transferable STSs as a medium of map definition and exchange. For those interested in gene searches, cytogenetic studies, etc., however, clone resources are

indispensible. Several approaches were proposed to satisfy the general needs. In addition to the extension of individual integrated reference activities (such as the Lehrach group at ICRF), several groups, starting with the Human Genome Centers at Washington University and Baylor College of Medicine and the Leiden group, have agreed to deposit sets of X-specific YACs at the American Type Culture Collection repository (Rockville, MD, USA). The ATCC repository would provide materials at nominal cost (per clone or per collection) in a manner analogous to its handling of lambda clones or bacterial plasmids in the past. With appropriate references to the literature and links to databases, this could give everyone an entree to useful current clones. The discussions acknowledged, however, that clones are transient, since "better" ones will become available with improvements in cloning technology, and new developments like long-range PCR could greatly change the entire way in which a map is stored and recovered, sharply reducing the dependence on stored banks of clones.

The definition of a finished map and its quality received some discussion in pointing toward the next phase of mapping efforts. The definition accepted for map completion by the U.S. NIH (100 kb resolution with ordered STSs and up to 100% continuity) is a demanding one, but offers a standard with markers stationed on average near every second or third gene, and near enough to permit easy recovery of new cognate clones of various types. Regions like portions of Xp22 (abs. 2 and 6), Xp11.21 (abs. 82) and most of Xq24-qter (abs. 54) already show that this standard can be achieved; and the Washington University Center reported a census of 1150 STSs from community and local efforts (abs. 55); this would provide at least 40% of the number required for the complete map of the X chromosome. In other efforts that assemble contigs on the basis of fingerprinting with inter-Alu or repetitive sequence probes, the contig coverage can be complemented with STSs derived from YACs or from independent sources. Along with the use of some YACs and probes in common, this provides a straightforward route to the integration of cloned coverage from various sources.

YACs are now providing long-range coverage of nearly all of the chromosome. In the longest stretch of DNA that is poorly cloned into YACs (about 1.5 Mb in subtelomeric Xq28), cosmids have been assembled (abs. 86) that provide the current map; and bacterial clones of various types (P1, BAC, PAC, etc.) can very likely provide comparable supplements to other more delimited zones of poor YAC coverage. Once again, the provision of resources is critical, particularly of high quality clones like the X-specific cosmid collection from the Lawrence Livermore Laboratory.

The next stage of efforts will involve the continuation of map closure while mapping merges increasingly with sequencing and gene-finding efforts. As in the case of long-range mapping, a number of approaches are currently being tested to verify maps and to reach analyses at higher resolution. They include comparative analysis of marker content in somatic cell hybrids and radiation hybrids (for example, Gorski et al., 1992; Peterlin et al., 1993), which can be combined with rare-cutter restriction mapping (O'Reilly et al., 1993); and the use of favorable patient material (Goyns et al., 1993; abs. 6). A fruitful approach to the higher resolution analysis of YAC-based contigs is to recover cosmids or other bacterial clones that provide another layer of the map, either by screening cosmid libraries or by subcloning YACs (abs. 5, 6 and 86; Holland et al., 1993; Buxton et al., 1993; Whitaker et al., 1993; Zuo et al., 1993).

Map assembly and closure can also be aided by comparative mapping. Progress on mapping of the mouse X chromosome was detailed by Brown and colleagues (abs. 10), by Boyd et al. (abs. 9), and by Pragliola et al. (abs. 60), including specific examples where information on clones in mouse was helpful to assembly of the human map. The current mouse X chromosome map has been summarized by Herman et al. (1994). Evolutionary comparisons in eutherian mammals and in marsupials are also useful to understand specific biological phenomena, such as X inactivation and sex determination (abs. 4, 17, 18 and 33).

YACs or cosmids provide substrates both for gene finding by a variety of means, including direct sequencing, with a useful modification of previous methods proposed by Fontes and colleagues (abs. 27). Such biological work clearly occupies a growing fraction of the attention of the community, both in respect to disease genes and in respect to genes in general. The placement of ESTs on the map (Parrish and Nelson, 1993) is now being abetted by searches for motifs and BLOCKs as mapping tools (D'Esposito et al., 1994), including the examination, for example, of cDNAs containing triplet-repeat elements (Li et al., 1993). The body of this report summarizes further some of the ongoing efforts to locate more genes, along with the first push toward long-range sequencing. About 600 kb of sequence has been accumulated in the last year, primarily from intervals in Xq27.3-q28 (see figure 2), and more extensive efforts are now beginning.

Genetic maps and new microsatellite polymorphisms

Several overall genetic maps of the X chromosome have been constructed. The initial Genethon map included 25 X-linked Afm microsatellite markers that are now well integrated with other markers in regional physical or genetic maps. The second generation Genethon map contains 80 Afm markers extending over 166 cM (Gyapay et al., 1994). Many of the new markers have also been integrated in YAC contigs or in various regional maps (see below and figure 1). These markers have also been used to screen the CEPH megaYAC library (Cohen et al., 1993). However, the Genethon map contains many clusters of unresolved markers, due to the relatively small number of CEPH families genotyped in that effort. The largest gaps have a length of 13 cM (in Xq24-q25) and 17 cM (in Xq27) (Gyapay et al., 1994). The latter may correspond to a region of higher recombination. The 236 cM map of Donnelly et al. (1994), initially reported at XCW4, contains 62 PCR-based marker loci, 30 of which were uniquely ordered in a framework map. Using data in the CEPH data base and genotypes generated on 15 CEPH families by the Cooperative

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Human Linkage Center (CHLC), Murray et al. (abs. 53) constructed three maps of increasing density, but decreasing confidence level. The "skeletal" map (143 cM) includes 23 loci, while the "framework" map contains 35 loci (206 cM) that overlap only partially with the 32 loci in the 210 cM map recently published by the same group (Buetow et al., 1994). The "comprehensive" map contains 150 loci (266 cM), including the new Afm markers, with questionable order of loci (since, at several places, the order contradicts well established physical or genetic maps described in previous reports). Yet another map (191 cM) generated from genotypes in the CEPH data base contains 24 uniquely ordered markers (15 of them from the first Genethon map), and 33 additional ones assigned to broader intervals (Matise et al., 1994).

While the effort involved in generating such maps is considerable, the density and reliability of the maps (and hence their usefulness) would be much improved if well-established order information derived from other sources (physical maps or genetic maps in disease families) was taken into account, as this would allow haplotyping of very close markers and would facilitate detection of genotyping errors. Genotyping of Afm markers in additional CEPH families would also help. However, as the order of most markers can now be resolved by physical mapping (on the YAC contigs), additional effort in pure genetic mapping might be directed to regions where the physical map is problematic (such a Xq24-q25) or to regions that appear to recombine much more than expected on the basis of their physical length (for instance the Xq27 region, that shows on all maps gaps of 10-20 cM).

In addition to the new Genethon Afm markers, more than 60 microsatellites have been developed since XCW4 and, where well-mapped physically, are included in figure 1. In particular, Barker and Fain (1993) developed and regionally mapped 23 polymorphic STSs for the Xp11-q22.1 region. These include nine CA repeats with greater than 50% heterozygosity and PCR assays for 11 previously known RFLPs (DXS262, 325, 326, 346, 347, 348, 349, 355, 356, 364, 441). CA repeats have also been characterised for other RFLP loci (DXS11, DXS100, DXS101).

Xpter - Xp22.1

The most significant advance in this region since the last report is the development of long range YAC-based physical maps for the majority of the region. Efforts by several groups to produce YAC-based contig maps have successfully bridged the majority of the region from the pseudoautosomal boundary to the region proximal to the POLA gene in Xp22.11. The consensus map (figure 1) indicates contiguity from DXS31 to DXS412, a distance estimated at 25 Mb. This contiguous stretch is the result of several different efforts, such that there are many different maps which underlie this consensus. While there is no single group which currently possesses contigs without gaps across this distance, clones and data are broadly available such that any interval of interest can be obtained. The largest scale effort was described by Ferraro et al. (abs. 6) with an estimated 40 Mb map extending previous work (Lee et al., 1993) in both directions from the pseudoautosomal boundary to the DMD locus. The map consists of 469 YAC clones assembled with 100 chromosomal breakpoints and 150 STSs. This set of contigs is separated by 5 gaps currently, and is annotated with a large number of known genes as well as anonymous expressed sequences. The data were presented in the SIGMA format.

Affara and colleagues (abs. 1) presented three YAC-based physical maps of the region. First, they reported a 500 kb contig across the Afm loci DXS996 and DXS1060 and encompassing a common distal breakpoint region found in three patients with chondrodysplasia punctata. The order of these two Afm markers differed from that presented by Ferraro which included a breakpoint and an EST in the interval. The Affara data were viewed as less compelling and differed from the order determined genetically by the Genethón group (Gyapay et al., 1994); thus the consensus map reflects the order pter-DXS1060-DXS996-qter. Affara's other maps encompass the DXS31 region (a small contig of indeterminate orientation) and the interval from distal to DXS1130 extending approximately 5 Mb to AMELX. This latter contig has been extensively mapped by pulsed-field gel (PFG) analysis, and the locations of numerous CpG islands were identified. Some 25 novel STSs were reported.

A very detailed YAC-based map of the 5 Mb region between DXS16 and DXS418 was presented by Alitalo et al. (abs. 2). This map encompasses several expressed sequences including XE59 (DXS1112E), GLRA2, PIGA, GRPR and CALB3. Transcriptional orientation of GLRA2 (pter to qter), PIGA (qter to pter) and GRPR (pter to qter) was also determined. 55 STSs were used to isolate and order 58 YACs. A subset was subjected to PFG analysis to provide detailed distance information and to indicate candidate regions for CpG islands.

Den Dunnen (abs. 25) presented three YAC contigs extending from DXS43 to DXS451, representing 17 loci. A discrepancy between the order of loci between this report and those of Ferraro, Ailitalo and Trivier (see below) was noted in the DXS69 to DXS418 region. While a consensus order was accepted from the three groups with similar order and orientation (figure 1), the discrepency is noted, and all groups will attempt to resolve the issue.

Hanauer (abs. 35) described construction of a YAC clone contig extending from DXS207 to DXS41 based largely on megaYACs and including a number of microsatellite markers, as well as some new STSs derived from YAC ends.

Francis et al. (abs. 28), in the course of refining the location of the HYP gene, described a contig of YACs across the DXS365 and DXS41 loci, a distance of approximately 1 Mb. Primers for a new microsatellite marker, DXS3424 were also described. This supplements efforts from the genetic perspective aimed at refining the location of HYP (Rowe et al., 1994). Currently (figure 1), the position of this disease locus is bounded by microsatellites DXS365 and DXS1683, a new marker recently described (Econs et al., 1994). This work is currently in press (Francis et al., 1994b). This group has also recently described a YAC contig spanning the interval between ZFX and POLA (Francis et al., 1994a).

Finally, the global YAC-based mapping report of Nagaraja et al. (abs. 55) described progress chromosome-wide, but included several contigs accreting in the Xp22 region.

In contrast to the important progress in the remainder of the region, the pseudoautosomal region actually took a step backwards from previous reports. Previously reports of YAC contiguity across the distal 2.6 Mb of Xp (Foote et al., 1992; Slim et al., 1993) have not borne out upon further analysis. In addition to missing the final 100 kb or so at pter, there are two known gaps in these contigs, one of approximately 300 kb near the CSF2RA ANT3 and IL3RA genes, and one of about 100 kb distal to the MIC2 gene. Rappold (abs. 62) presented analysis of this region and of additional YACs in an effort to establish contiguity. Significant gaps still remain and these have been introduced into the consensus map (figure 1). The other presentation in the pseudoautosomal region was also from Rappold (abs. 63), reporting an apparent double recombination in the PAR in a male meiosis. An excellent review of this region was recently published (Rappold, 1993), and further detail can be found in the report of the first Y chromosome workshop.

Ballabio (abs. 5) described a method for establishing cosmid clones using YAC contigs as probes in a flow-sorted X-specific cosmid library developed at Lawrence Livermore National Laboratories. Clones are assigned to bins using whole YAC as well as restriction fragments and hybridization. This resulted in the collection across the OA1 to MLS interval of 139 cosmids spanning 1.6 Mb organized into 17 bins (average 75 kb) and 9 contigs. A minimal spanning set of 53 clones was identified. The longest contig was 665 kb in length. Gaps remaining in the map were estimated at less than 7%.

Physical mapping in hybrids continued in addition to that reported in YACs. Hanauer and colleagues (abs. 94) described refined locations for four genes and two ESTs using a panel of hybrid cell lines including some radiation hybrids. The orders of markers and genes (CALB3, GRPR, GLRA2 and PDHA1) were consistent with orders reported by YAC-based efforts. One EST (DXS1118E) was consistent with placement on the YAC contig from Ferraro et al. (abs. 6). The other EST (DXS1006E) has not been integrated into the YAC-based maps as yet, but no doubt will be quickly positioned. Hors-Cayla et al. (abs. 38) described a panel of radiation hybrids used to order markers in the DXS278 to DXS28 interval, including a large number of genetically useful microsatellites. The order described was not inconsistent with those reported by the YAC-based mapping projects. Recombinant chromosomes identified in families segregating the SEDL locus refined the position of this disease gene (Heuertz et al., 1993) between DXS987 and DXS16, while also demonstrating order relationships between several informative markers (DXS92-DXS41, DXS1224-DXS16, DXS1229-DXS1226) with other crossovers.

Several new genes and expressed sequences have been described in this region of the X since XCW4. The PBDX gene, spanning the pseudoautosomal boundary, is an excellent candidate for the XG blood group (Ellis et al., 1994). A new member of the voltage-gated chloride channel gene family was recently identified in the region near the OA1 gene (van Slegtenhorst et al., 1994). This gene spans 60 to 80 kb and lies immediately proximal to the candidate region for OA1, but is unlikely to be the gene responsible for that phenotype. A new cDNA derived from a retinal library and mapping the Xp22.1-p22.2 was described (abs. 76). The structure of the CALB3 gene, located immediately proximal of DXS43, was recently determined (Jeung et al., 1994); it is a small (5.5 kb) gene composed of three exons. The position of the SAT gene has been refined distal to ZFX (abs. 6), while an additional EST (DXS1115E) positioned in the ZFX-POLA interval. The region is currently known to contain 27 cloned genes and ESTs (see figure 1 and Genome Data Base).

Refined locations of several disease genes were reported. Chondrodysplasia punctata (CDPX) has been suggested to be located in an interval defined by chromosome rearrangements of 400 kb by Rappold and coworkers (abs. 64) (Klink et al., 1994). Complex phenotypes were observed in two male patients with terminal rearrangements of Xp (abs. 30). These deletions extended to between DXS143 and KAL in patient 1, and to between DXS278 and DXS237 in patient 2. Distal boundaries are not yet certain. OA1 and MLS have more refined locations based on deletion analyses and additional chromosome breakpoints (figure 1) (abs. 5,6). A report in press from Hanauer describes a balanced X;9 translocation associated with hypomagnesemia with secondary hypocalcemia (HOMG) in a female and fine localization of the Xp22 breakpoint to between DXS16 and DXS207/DXS43 (Chery et al., 1994). The RS gene is currently localized between the markers DXS207 and DXS1053 distally and DXS999 proximally (abs. 83), while the CLS gene is refined to between the new marker DXS1683 and an Afm microsatellite currently known as Afm 291wf5. A Spanish family was described (abs. 29) with non-syndromic X-linked mental retardation exhibited linkage to DXS85 with a zmax of 2.28 and a theta of zero (abs. 29). This locus has been termed MRX24. Finally, the limits of the KFSD locus were determined by Den Dunnen and colleagues to be between DXS418 distally and DXS274 proximally (abs. 24).

Xp21.3 - Xp11.23

In Xp21.3, Ferraro et al. (abs. 6) have linked YAC contigs containing DXS68, DXS67, DXS669 and DXS28 (Walker et al., 1991) to the more proximal AHC-GK-DMD contigs (Walker et al., 1992; Worley et al., 1993), using two smaller YAC contigs surrounding a Rett syndrome translocation (Ellison et al., 1993). This provides a complete contig of Xp21.3 and a locus order of pter-(RDXP2, DXS68)-DXS67-DXS669-DXS28-DXS1086-DXS1101-DXS1147-DXS1149-DXS1088-DXS727-DXS1074-DXS319-DXS1075-DXS1076-DXS1077-DXS708-GK5'-DXS1078-GK3'-DXS1079-DXS1080-DXS1081-DXS726-DMD3'-cen (Fig. 1). A 160 kb region around DXS319 was found to be duplicated in sex-reversed XY females (abs. 12). The responsible locus has been named DSS (for *Dosage Sensitive Sex-reversal*). The DSS region partially overlaps the critical deletion interval for adrenal hypoplasia congenita (AHC).

All the dinucleotide repeat polymorphisms in the DMD region have been given DXS numbers and are indicated on the consensus map, along with loci that designate important deletion or translocation breakpoints. The bridging YAC contig of Xp21.3 described above (abs. 6) and the previously reported DMD YAC contigs (Monaco et al., 1992, Coffey et al., 1992) provide contiguous YAC coverage of the Xp21.3-Xp21.2 region from DXS68 to DXS84. Nagaraja et al. (abs. 55) have used existing and newly isolated YACs to generate a 5.1 Mb YAC contig of the Xp21.3-p21.2 region. They have also tested many Généthon markers and located DXS1214, DXS1219, DXS1036, DXS1067, DXS997, and DXS992 within this YAC contig.

In Xp21.1, the existing 1.7 Mb YAC contig containing pter-DXS709-CYBB-DXS140-DXS1082-OTC-cen (Ho et al., 1991) has been extended 1.1 Mb proximally by Carvalho et al., (abs. 46) to include DXS352 and DXS1068. Two new genes have been isolated in Xp21.1 region around the CYBB gene. The gene for McLeod syndrome (XK) has been identified distal to CYBB, using YAC and cosmid contigs and information from a McLeod patient with a 50 kb deletion (Ho et al., 1994). The XK gene encodes a novel transport protein with 10 potential transmembrane domains. The XK gene is expressed as a 5.2 kb mRNA in fetal liver and spleen, adult brain, heart, skeletal muscle and pancreas and is predicted to encode 444 amino acids. The XK gene spans ~30 kb of genomic DNA and is organized into three exons transcribed from telomere to centromere. Proof that it was responsible for McLeod syndrome came from the identification of splice site mutations in two non-deletion McLeod patients (Ho et al., 1994).

A new gene has been isolated from a CpG island 180 kb proximal to CYBB and found to hybridize to a 2.1 kb mRNA in many tissues (Roux et al., 1994). The gene, which is located ~30 kb distal to the BB deletion breakpoint, spans 9 kb and is organized into five exons transcribed from telomere to centromere. The predicted 116 amino acid sequence has a high degree of similarity to the tctex-1 gene of the murine t complex. This region proximal to CYBB has been implicated in retinitis pigmentosa (RP3) from deletion analysis. Therefore, the Xp21.1 tctex-1 like gene was tested for structural and sequence abnormalities in 20 RP3 patients, but none were found. Genetic linkage analysis in RP3 families using a dinucleotide repeat polymorphism (DXS1110) in the fourth intron of the tctex-1-like gene indicates that the RP3 gene is located more proximally, yet still distal to OTC (Roux et al., 1994). The estimated distance between CYBB and OTC is 450 kb based on a YAC map (Ho et al., 1994), and since the tctex-1-like gene is 180 kb proximal to CYBB, the RP3 critical region is now narrowed to approximately 270 kb between the tctex-1-like gene and OTC (figure 1).

Carvalho et al. (abs. 46) have isolated several new dinucleotide repeat polymorphisms (DXS6678, DXS6680, DXS6679 and DXS1368) in the Xp21.1-p11.4 region and provided order based on genetic linkage analysis as pter-DXS84-(DXS6678,DXS6680)-CYBB-(DXS6679,OTC, DXS352)-DXS1068-DXS361-DXS556-DXS1368-DXS993-DXS7-cen. Linkage analysis in 24 X-linked retinitis pigmentosa families using these markers define a candidate interval between (DXS6678,DXS6680) and DXS361.

Combining both the physical and genetic mapping data in the Xp21.1-Xp11.4 region provides a consensus order of pter-DXS84-(DXS141,DXS307)-DXS709-(DXS6678,DXS6680)-XK-CYBB-DXS140-(tctex-1-like,DXS1110) (DXS6679,OTC, DXS352)-DXS1068-DXS361-DXS556-DXS1368-DXS993-DXS228-DXS77-DXS7-cen, as shown in figure 1.

In Xp11.4-p11.3, Black et al. (abs. 19) have expanded a 650 kb DXS7 YAC into a contig of 19 YACs containing the following markers and genes: pter-DXS1201-DXS6668-DXS228-DXS77-DXS6669-DXS7-MAOA-MAOB-NDP-DXS6670-RRM2P3-DXS6671-DXS742-cen. This contig contains the BXP136 translocation breakpoint (t75-2ma-1b) positioned close to the 5'-end of the MAOB gene. Another YAC contig in the same region has been constructed by Berger et al. (abs. 71). This 1.5 Mb YAC contig contains the following order of markers: pter-DXS7-MAOA-MAOB-NDP-F9/4-DXS1707-DXS1708-cen. In the same abstract they reported linkage analysis in congenital stationary night blindness (CSNB1) families showing no recombination with DXS228, MAOB and NDP with the critical interval between MAOA and DXS1003. Since the Norrie's disease gene (NDP) is in the CSNB1 critical region, they tested for point mutations, but failed to find any sequence alterations in the coding region and splice sites. Another linkage study has shown a different critical interval (DXS426 to DXS1000) for a large family segregating CSNB1 (Bech-Hansen and Pearce, 1993; Bech-Hansen et al., 1993). This suggests possible locus heterogeneity for X-linked CSNB in Xp11. A recent paper performing genetic linkage analysis in a new family segregating Åland Island eye disease (AIED) helps to define a critical region for AIED between DXS7 and DXS255 (Glass et al., 1993). This interval overlaps with both minimal regions suggested for X-linked CSNB.

In Xp11.23, large YAC contigs constructed by several groups have been linked together from DXS1264 to DXS1240. These include a 1.9 Mb contig from Coleman et al. (1994 and abs. 16), Knight et al. (1994), and Hagemann et al. (1994), suggesting the following consensus order of loci: Xpter-DXS1264-DXS1055-DXS1003-DXS1146-DXS1266-ARAF1-SYN1 CA repeat-SYN1/3'end-TIMP1-SYN1/5'end-PFC CA repeat-PFC-(DXS426, ELK1)-(DXS1265, ZNF81)-ZNF21-DXS1267-DXS6616-OATL1-cen. In addition, Coleman et al. (abs. 16) mapped ZNF41 between DXS1266 and ZNF81 and placed UBE1 distal to their large DXS426 contig in a set of independent YACs. However, Hagemann et al. (1994) found UBE1 within a similar contig distal to ARAF1. Thus, while the relative location of UBE1 is confirmed, its connectivity to the Xp11.23 contigs requires further study. Coleman et al. (abs. 16) have also constructed a smaller unoriented contig proximal to OATL1 containing the following order of markers: (GATA1-DXS226-DXS1126-DXS1240).

Additional contigs and important links between contigs in this region were reported (abs. 13, 20, 36 and 95). Fisher et al. (abs. 20) constructed a YAC contig linking GATA1 with OATL1 with the following order: pter-OATL1-DXS6663-DXS6664-GATA1-DXS6665-cen. They also constructed

another contig linking TFE3 and SYP and a third 2.2 Mb YAC contig linking DXS255 and DXS146 with the following probe order: pter-DXS6666-DXS255-DXS146-DXS6667-cen. Kamakari et al. (abs. 36) have partial YAC contigs giving the following order of markers: pter-UBE1-DXS1055-DXS1003-TIMP1-SYN1-PFC-DXS426-OATL1-MG61-DXS722-GATA1-DXS226-DXS1126-SYP-DXS255-cen. Meindl et al. (abs. 47) used a combination of YACs, radiation hybrids and genomic PFG analysis to order markers as pter-DXS337-TIMP1-PFC-ELK1-DXS1367-OATL1-(GATA1, DXS226, DXS1126)-TFE3-DXS255-DXS146-cen. DXS1367 is a new CA repeat isolated from a PFC-ELK1-positive YAC that provides a new flanking distal marker for Wiskott-Aldrich syndrome (WAS), with DXS146 as the proximal flanking marker in the present study. They also isolated a novel expressed sequence (R1) which maps between ELK1 and PFC. Genomic PFG mapping showed physical linkage of the GATA1, DXS226, DXS1126 cluster to TFE3 on a 650 kb NotI fragment, and SYP linked more proximally to DXS255 and DXS146 on a large >2 Mb NotI fragment. This provides preliminary orientation of TFE3 as distal to SYP. In summary, Meindl et al. (abs. 47) placed the WAS critical region between DXS1367 and DXS146 with an estimated distance between 2.5-3.5 Mb. Previous publications have shown a recombinant in one WAS family that places the WAS locus distal to DXS255 (Kwan et al., 1991; Cremin et al., 1993). DXS255 is estimated to be about 600 kb distal to DXS146 in the YAC contig of Fisher et al. (abs. 20).

Bech-Hansen et al. (abs. 95) mapped a series of new repeat polymorphisms, ESTs and STSs on a panel of radiation and conventional hybrids which define 14 intervals in Xp11. They found that DXS1004E and DXS1007E mapped to previously isolated YACs, consistent with their homology (identity) to ZNF41 and SYP, respectively. Another YAC contig linking SYP and TFE3 was found to have markers and genes in the following order based on the location of the BXP138 (SIN176) deletion breakpoint: pter-DXS6674-DXS6675-DXS1011E-BXP138-DXS6676-SYP-TFE3-Xp664-cen. The order of SYP and TFE3 in this map is in contrast to the genomic PFG data of Meindl et al. (abs. 47) and needs further clarification.

Overall, the consensus order of markers and genes in the Xp11.4-Xp11.23 region is pter-DXS993-DXS1201-DXS6668-DXS228-DXS77-DXS6669-DXS7-MAOA-MAOB-NDP-DXS6670-RRM2P3-DXS6671-DXS742-UBE1-DXS1264-DXS1055-DXS1003-DXS1146-DXS1266-ARAF1-SYN1-TIMP1-PFC-(DXS426,ELK1)-DXS1367-ZNF81-ZNF21-DXS1267-DXS6616-OATL1-MG61-DXS722-GATA1-DXS226-DXS1126-DXS1240-DXS1011E-(TFE3,SYP)-DXS6666-DXS255-DXS146-DXS6667-OATL2-cen (figure 1).

To isolate new genes for the identification of the Wiskott-Aldrich syndrome, Kolluri et al. (abs. 40) used a 420 kb TIMP1 YAC for cDNA selection experiments. This YAC contains the known genes ARAF1, SYN1, TIMP1, PFC, and ELK1 which comprised 60% of the cDNA selection sublibrary. The remaining 40% were novel cDNAs, of which four were hybridized to Northern blots to determine expression patterns and mapped back to restriction digests of the YAC to place them relative to known genes.

Mapping of two different X-linked renal tubular disorders has suggested independent locations within Xp11 (abs. 77), as already reported at XCW4. Analysis of unrelated families with Dent's disease showed no recombination with markers ARAF1, DXS426, and DXS255. In addition, a microdeletion was found in one family with the DXS255 locus, thus confirming the Xp11.22 location (Pook et al., 1993). Fisher et al. (abs. 20) have isolated a cDNA clone within 40-80 kb of DXS255 that is highly expressed in kidney. It is a potential candidate gene for Dent's disease and has amino acid similarity to chloride ion channels. X-linked recessive nephrolithiasis (XRN) is a renal tubular disorder associated with recurrent calcium kidney stones and proteinuria in childhood, and nephrocalcinosis and renal failure in adulthood. Preliminary genetic linkage mapping had shown XRN to be located in a relatively large interval between DMD and DXS255 (Scheinman et al., 1993). Thakker et al. (abs. 77) have used a larger number of polymorphisms and now show the highest peak location score in the interval between MAOB and (ARAF1, DXS426) in Xp11.23. Therefore, Dent's disease and XRN seem to have separate locations in Xp11 and are most likely not allelic mutations of the same gene.

Eight human genes from Xp11 were used in comparative mapping studies to locate their homologues in a marsupial and a monotreme species. Wilcox et al. (abs. 33) found that UBE1, ALAS2, and GATA1 are on the X in marsupials and monotremes, suggesting that the centromere and the most proximal region of the human X is part of the ancestral X chromosome. ARAF1 is on the X in marsupials, but is autosomal in monotremes, while TIMP1, SYN1, OATL1 and MAOA are autosomal in both. This suggests that these genes lie in the more recently added region with the evolutionary fusion point located in Xp11.23 region. However, the UBE1 gene in human is thought to be distal to both ARAF1 and TIMP1 and in marsupials has a Y homologue, indicating that the situation may not be simply explained by one ancestral breakpoint.

Xp11.22 - Xq13.3

As with other regions of the chromosome, this region has benefitted from the coordination of efforts between major genome centers and individual laboratories focussing on particular areas of interest. The abstract of Nagaraja et al. (abs. 55) and various abstracts representing work from or in collaboration with the Monaco group should be consulted in this regard.

Complete integration of the physical and genetic maps remains incomplete and problematic, as discussed in a general context in a section above. The genetic order of some markers in the Xp11.22 to q13.3 region reported by Murray et al. (abs. 53) is clearly inconsistent with established physical order. The general problem of integration in this region is also heightened by the clear reduction of recombination observed in the vicinity of the X chromosome centromere. Most genetic maps report a distance of only a few cM from DXS991 (in a contig in

Xp11.21) to AR (in Xq12) or DXS106 (in Xq13.1), spanning a physical distance of >10 Mb.

Miller et al. (abs. 82) described a ~5 Mb YAC contig spanning Xp11.22-p11.21 and including genes for pter-OATL2-DXS6672E-DXS1272E (XE169; Wu et al., 1994)-DXS423E-DXS1013E-ALAS2-ZXDB-ZXDA-cen and a number of widely used microsatellite markers (DXS1000, DXS988, DXS1199 and DXS991). The order of these markers suggested by YAC contigging (abs. 82) or by genetic linkage analyses (abs. 95) is consistent. The distal end of the contig subsumes a 1.9 Mb contig containing DXS423E, DXS1199, DXS988, DXS1000 and DXS1206 (abs. 55). The proximal end of the contig subsumes a 2 Mb YAC contig described by Reed et al. (1994) that includes the DXF34 family (all members of which map to a region of <100 kb), duplicated copies of DXS390, and the duplicated zinc finger protein genes ZXDA and ZXDB initially isolated by Greig et al. (1993). Boyd et al. (abs. 9) reported a cDNA for the DXF34S1E locus. The most proximal Xp region has undergone considerable rearrangement during evolution, as the homologous sequences on the mouse X chromosome map to at least four different regions (Blair et al., 1994). Interestingly, the most proximal human sequences examined (DXF34) have murine homologues adjacent to the mouse X centromere, suggesting that the DXF34-centromere linkage is conserved between human and mouse. None of the reported contigs include alpha satellite DNA at the centromere (DXZ1), and the distance between the most proximal marker ZXDA and DXZ1 is estimated to be < 500 kb on the basis of interphase fluorescence in situ hybridization experiments (abs. 82). In light of this, it would be of obvious interest to regionally map the murine homologues of ZXDA and ZXDB.

The DXZ1 locus at the centromere is known to span ~3 Mb (range 1.5 - 4 Mb on different X chromosomes) (Mahtani and Willard, 1990). Initial efforts to isolate sequences from the junction(s) between alpha satellite and the chromosome arms have now been reported (Bayne et al., 1994; abs. 82). Bayne et al. isolated sequences from an X chromosome deleted at the centromere, caused by telomere-associated fragmentation. Interestingly, the sequences so identified were not "typical" X chromosome alpha satellite (DXZ1), but rather diverged alpha satellite sequences in an inverted orientation (Bayne et al., 1994), as found previously for the chromosome 7 centromere (Wevrick et al., 1992). Similar diverged sequences have also been isolated in a YAC that maps to the X centromere (abs. 82).

On the Xq side of the centromere, a series of YAC contigs have been described in the region between Xq11.2 and PGK1 (in Xq13.3) (abs. 8, 27, 49, 55 and 82). The most proximal gene is that for moesin (MSN; originally identified as DXS1117E), which has been mapped to Xq11.2 by several groups (Wilgenbus et al., 1994; Parrish and Nelson, 1993; Kishino et al., 1994; abs. 82) and is included in a YAC contig proximal to DXS1 and AR (abs. 82). Moesin is a member of a family of closely related proteins, including ezrin, radixin, and the neurofibromatosis 2 product, merlin, and is believed to be important for cell-cell recognition and cell movement. The MSN gene consists of 12 exons distributed over 30 kb in Xq11.2 (Wilgenbus et al., 1994). Exon/intron boundaries and the nature of the 5' end have been determined. The gene is widely expressed (Wilgenbus et al., 1994) and is subject to X inactivation (abs. 82).

A 1.3 Mb contig described by Nagaraja et al. (abs. 55) includes GJB1 and CCG1, a region that is also included in a YAC contig by Villard et al. (abs. 27). These contigs also overlap ones described by Rider et al. (abs. 49) in Xq12 - q13.1 and by Bone et al. (abs. 8) in Xq13.1. There was some disagreement on whether these contigs could be connected to the previous one described by Lafreniere et al. (1993) in Xq13.2. One clear discrepancy (the placement of DXS559 with respect to GJB1 and CCG1) requires resolution. Somatic cell hybrid data (Lafreniere et al., 1991) indicated that DXS559 maps proximal to DXS131, in agreement with the YAC content data of Villard et al. (abs. 27), who reported the order GJB1-DXS559-CCG1-DXS131. YAC data of Bone et al. (abs. 8), however, indicate the order GJB1-CCG1-DXS559. Bone et al. also mapped the IL2RG gene (involved in X-linked severe combined immunodeficiency) proximal to GJB1 and CCG1 in their YAC contig. This orientation has not yet been confirmed by independent studies.

A more distal 2.1 Mb contig (Villard et al., abs. 27) in Xq13.3 contains 12 YACs and closes a previous gap in the YAC map, which now spans DXS441 to PGK1 and confirms the order of markers suggested by earlier PFG studies (see Schlessinger et al., 1993). New cDNAs were isolated from this contig by Gecz et al. (abs. 31) using direct selection with YAC clones from the region. This 2.1 Mb region contains up to 10 genes, including those for PGK1 and ATP7A (Menkes disease). Newly assigned genes include those for an X-linked nuclear protein (DXS6677E; also described as XNP; Gecz et al., 1994) and a previously isolated gene for ribosomal protein S26 (abs. 31).

Wu et al. (1994) described cDNAs for a novel gene that escapes X chromosome inactivation. The gene, XE169 (also called DXS1272E), encodes a ~1560 amino acid protein with localized homology to a retinoblastoma-binding protein, RBP2. XE169 was originally assigned to the proximal half of Xp by Wu et al. (1994) and has been finely mapped by Miller et al. (abs. 82) on the YAC contig in Xp11.22 - p11.21 between OATL2 and DXS423E. This is in the vicinity of one class of chromosome breaks found in synovial sarcoma (see previous reports; Schlessinger et al., 1993; Willard et al., 1994), and, in light of the homology to RBP2, it would be of interest to evaluate XE169 in these tumors. Agulnik et al. (1994) have independently cloned the same gene and called it SMCX. The mouse homologue of XE169/SMCX also escapes X inactivation (Agulnik et al., 1994).

Greig et al. (1993) described the isolation and sequencing of two highly similar zinc finger protein genes, ZXDA and ZXDB, in Xp11.21. Both genes are expressed widely in different tissues and both are subject to X inactivation. The predicted proteins differ in only a single amino acid within 10 zinc finger motifs of the Cys_2-His_2 type. The duplicated genes map ~400 kb apart, as shown by Miller et al. (abs. 82).

Zonana et al. (abs. 85) and Kere et al. (abs. 39) described continuing progress towards identification of the hypohidrotic

ectodermal dysplasia (EDA) gene in Xq12. Several small deletions have been identified in different patients and a number of candidate cDNAs are under active investigation. Zonana et al. described a cDNA for DXS732E, which is located proximal to the EDA translocation breakpoints (BXP162 and BXP179), but appears not to be disrupted.

Since the last meeting, X-linked Charcot-Marie-Tooth disease has been found to be due to mutations at the GJB1 locus, as described first by Bergoffen et al. (1993). Additional mutations have now been reported by Fairweather et al. (1994), Ionasescu et al. (1994), and Bone et al. (abs. 8). These data are consistent with the refined genetic mapping of Charcot-Marie-Tooth disease on additional families (Fain et al., 1994).

Van der Maarel et al. (abs. 68) have cloned a gene, DXS6673E, that is a candidate gene for X-linked mental retardation in Xq13.1, originally identified by the presence of an X;autosome translocation in a mentally retarded female. This could be the same as one of the X-linked mental retardation genes previously mapped to the pericentromeric region (Schwartz, 1993; Passos-Bueno et al., 1993; abs. 69; Willems et al., 1993; Hu et al., 1994). The breakpoint was localized between (GJB1,IL2RG) and CCG1 and cloned. Candidate cDNAs have been isolated, but no mutations in karyotypically normal patients with X-linked mental retardation have been found to date. The sequenced portions of the DXS6673E cDNA show no detectable homology with previously described genes.

Genetic linkage analyses have also refined localization of the dystonia-parkinsonism syndrome locus, DYT3, to between DXS106 and DXS559 in Xq13.1 (Wagner et al., 1994). Since this region is fully contained in the YAC contigs described above, positional cloning of the gene should now be possible.

A gene originally detected with the anonymous probe for DXS128 in Xq13.2 has been cloned and characterized by Lafreniere et al. (1994). The gene consists of eight exons distributed over 150 kb, encodes a transmembrane protein with a PEST domain at the N-terminus, and shows homology with a family of transport proteins. The gene has been designated XPCT (X-linked, PEST-containing transporter). XPCT is subject to X inactivation, which is notable because it maps only ~600 kb distal to the XIST gene, whose inactive X-specific expression has been implicated in X inactivation.

The X inactivation center (XIC) has previously been localized to a ~1 Mb region in Xq13.2 between the breakpoints BXP144 and BXP199 (see previous reports; Schlessinger et al., 1993; Willard et al., 1994). There has been no further refinement of this assignment, although mapping of several new structurally abnormal X chromosomes (abs. 48) is consistent with the prior assignment. Several reports have examined the putative role of XIC in X inactivation. Rack et al. (1994) and Brown and Willard (1994), using isodicentric or deleted X chromosomes in leukemia or in somatic cell hybrids, respectively, demonstrated that the XIC and the XIST gene are not required for on-going maintenance of the inactive and late-replicating state of the inactive X chromosome. This supports a role for the XIC in initiation of X inactivation, but offers no clues as to the constitutive expression of XIST in somatic cells (see recent review by Heard and Avner, 1994). The possibility of control elements important to X inactivation, within the XIC but distinct from the XIST gene itself, is suggested by linkage studies in the mouse that mapped the Xce locus distal to Xist (Simmler et al., 1993), by methylation studies distinguishing between the active and inactive X's in the mouse (abs. 4) and by studies demonstrating a failure of X inactivation in patients with small centric ring X chromosomes (Migeon et al., 1993; Wolff et al., 1994), despite, in a few exceptional cases, retaining a copy of XIST on the ring chromosome (Migeon et al., 1993).

Previous reports have discussed the assignment of a locus, IP1, for sporadic incontinentia pigmenti associated with structural abnormalities of the X chromosome (Schlessinger et al., 1993; Willard et al., 1994). Given the clear differences between the skin abnormalities noted in these patients and those with classical IP, as well as the wide distribution of breakpoints associated with this phenotype, it now seems possible that the clinical findings represent functional disomy of one or more genes in this region associated with incomplete non-random X inactivation, rather than, as originally hypothesized, defects at one or more genes found at the site of the rearrangements. Indeed, such functional disomy (due to a failure of X inactivation) has been demonstrated for centric r(X) or mar(X) chromosomes associated with severe phenotypes (Migeon et al., 1993; Wolff et al., 1994), at least a few of whom have clinical symptoms consistent with the skin abnormalities noted previously. Given this uncertainty about the existence of a discrete locus in this region with any relationship to IP, we have removed IP1 from the consensus map figure.

Xq21 - Xq22

Previously, the Xq21 region was mapped in detail by making use of a large number of deletions and X;autosome translocations (see previous reports; Schlessinger et al., 1993; Willard et al., 1994). Recent reports have described the construction of several YAC contigs across Xq21, including the X-Y homologous region. Extensive YAC cloning in Xq22 has resulted in sizeable YAC contigs encompassing most of this chromosomal segment. A number of microsatellite markers have not yet been accurately mapped in this chromosomal segment. Since only a few disease entities are known to reside in Xq21, functional studies have concentrated on positional cloning of disease genes rather than on construction of a transcript map.

A framework for Xq21 mapping was published by Philippe et al. (1993) with 20 intervals subdividing the Xq21 region. A total of 55 DNA markers, including many (CA)n-dinucleotide loci, have been positioned in Xq21 (abs. 93). The location of three microsatellite markers in Xq21 (DXS986, DXS995, and DXS1002) was corroborated by Jani et al. (abs. 48).

Xq21 YAC cloning has been concentrated on three regions. In Xq21.1, Dahl et al. (abs. 23) and Huber et al. (F. Cremers, personal communication) isolated overlapping YAC clones spanning DXS169, DXS26, and DXS995. Both groups have identified microdeletions associated with X-linked mixed

deafness (DFN3). Dahl et al. identified a microdeletion spanning DXS169 and extending in the centromeric direction. Huber et al. constructed a 850 kb cosmid contig spanning DXS995 and DXS26 and were able to identify a total of four microdeletions associated with DFN3. At least two DFN3-associated microdeletions do not overlap syndromic DFN3 deletions. Together, these data suggest the existence of a very large gene (> 700 kb) involved in DFN3 or the presence of at least two DFN3 genes in this chromosomal interval.

In the Xq21.31-q21.32 region, Stanier et al. (abs. 75) identified 75 YACs with markers from the critical region for cleft lip and palate (CLP), as defined by genetic linkage analysis. This region is demarcated by DXS1002 at its proximal and DXYS1 at its distal side. A 3.5 Mb YAC contig encompassing DXS1002, DXS95, DXS1196, DXS262, DXS110, DXS1066, DXS472, and DXS1169 was established. This contig does not yet link up with several YACs isolated with DXYS1 (figure 1).

Making use of the published Y chromosome YAC contig, Mumm et al. (abs. 52) and Sargent et al. (abs. 72) constructed six relatively small YAC contigs containing 40 X-Y homologous markers, totalling ~3 Mb in size. The most proximal contig comprises DXYS1. In the physical map, only seven markers are indicated. Since at least one marker (DXS214) has been positioned in this region, it probably is non-continuous (Philippe et al. 1993). Just distal to this region, a small YAC contig spanning DXS3 and DXS1203 was presented (abs. 55).

In Xq22, a comprehensive YAC contig comprising 33 DNA markers and spanning 6.5 Mb was published (Vetrie et al. 1994). This contig includes the genes involved in X-linked agammaglobulinaemia (BTK), Fabry disease (GLA), and Pelizaeus-Merzbacher disease (PLP). The order of markers in this contig is consistent with the known genetic and physical mapping information of Xq22. Additional YAC contigs just proximal to this region encompassing DXS118-DXS122-DXS174-DXS1231 and DXS366-DXS454 were identified by Srivastava and coworkers (D. Schlessinger, personal communication). Finally, in Xq22.3, a 1.7 Mb YAC contig containing COL4A5, COL4A6, DXS137, and DXS1105 has been established (Vetrie et al. 1992; abs. 55).

Schwartz et al. (abs. 73) described a third family with Allan-Herndon-Dudley syndrome (AHDS). Linkage analysis with DXS326 resulted in a maximal lod score of 4.2 with no recombinations observed. DXS326 is located near the critical region for a XLMR gene between DXS26 and DXS121 which was formerly defined by deletion mapping in the Xq21 region (abs. 93). AHDS recombines distally with DXYS1 and proximally with DXS1111, a marker yet to be positioned physically. The AHDS locus therefore might be located proximal to the Xq21 region known to be deleted in patients with MR, DFN3 and CHM.

The complete open reading frame of the choroideremia (CHM) gene has been cloned (abs. 21). It spans 15 exons encompassing a minimum of 150 kb. Among 75 classic CHM patients, 15 deletions were identified, only two of which are intragenic. The others extend both proximally and distally, some of which are up to 15 Mb in size. A second X-autosome translocation (patient TDo) has been shown to disrupt the CHM gene between exons 3 and 4 (abs. 21 and 93). Two microsatellite markers from within the CHM gene, a (CA)n-dinucleotide and a more complex (AT)n-like repeat were described (abs. 21). Both markers should be useful for diagnostic studies in CHM families.

A patient with X-linked agammaglobulinaemia (XLA), torsion dystonia and X-linked sensorineural deafness showed a deletion of the 3´ part of the BTK gene (formerly atk or BPK), extending centromerically into a flanking gene FCI (Vorechovsky et al., 1994). Gal and coworkers (personal communication) studied a Norwegian family with X-linked deafness and some additional clinical features (DFN1; Mohr and Mageroy, 1960). Linkage analysis positioned the DFN1 gene in Xq22 between DXS454 and COL4A5. FCI, therefore, is a candidate gene for DFN1 but might also be responsible for X-linked sensorineural deafness in those families that are not linked to Xq21 (Reardon et al. 1991).

A study by Saugier-Veber et al. (1994) described the identification of a mutation in the PLP gene in at least one clinically distinct form of X-linked spastic paraplegia (SPG2), suggesting that Pelizaeus-Merzbacher disease and SPG2 are allelic disorders.

Zhou et al. (1993) identified deletions that disrupt both the COL4A5 and the COL4A6 genes in patients with Alport syndrome as well as diffuse leiomyomatosis, a rare condition characterized by benign smooth muscle cell proliferation. Thus, type IV collagen may regulate smooth muscle differentiation and morphogenesis.

Xq24 - Xqter

YAC contigs that total in excess of 50 Mb have covered essentially all of the region for more than a year (Schlessinger et al., 1993), but the closure phase of mapping in this region is slow and demanding. Nevertheless, substantial progress has been made to increase the resolution of the map and complete the coverage. Contigs have been aligned and oriented across the entire region, with nine remaining gaps in Xq24-q26.1 and two in Xq26.1-qter defined and still under investigation. A total of 353 STSs have been placed in the region, with more than half unambiguously ordered, so that the goal of 100 kb average inter-STS distance is within reasonable reach.

Concerning the integration of physical and genetic data, YACs have been recovered for all published markers that detect polymorphism, and all but two have been placed in contigs (figure 1). Functional mapping is also progressing, with 15 Mb of the region extensively mapped with rare-cutter enzymes (Pilia et al., 1993; abs. 26), and many of the CpG islands recovered for further analysis. Finally, substantial sequencing in the Xq27.3-q28 region has begun.

Starting from the telomere, Xq28 has now been extensively mapped by two groups (figures 1 and 2). Using STS content mapping supplemented with the use of hybridization probes and rare-cutter mapping, Palmieri et al. (abs. 26) have mapped 7.1 Mb of the region in a series of contigs based on YACs and some cosmids from the collections of Tsuji et al. and Poustka et

al. (see Schlessinger et al., 1993). Verification methods included the internal consistency of the contents of 152 hybridization probes and forty-one CpG islands (the latter identified on the basis of the near-coincidence of at least three rare-cutter restriction enzyme sites containing CpG dinucleotides). The most centromeric 1 Mb region is merged into a large contig across Xq27 (see below), followed by, successively, about 3.2 Mb of moderate GC content and CpG island content through the GABRA3 locus; 1.5 to 2 Mb, extending to the G6PD gene, that is variably and poorly cloned, but contains a high concentration of CpG islands and GC; and about 1.5 Mb from G6PD to Xqter, which is low in CpG content and GC.

Rogner et al. (abs. 89) have independently mapped Xq28 into three YAC contigs, encompassing about 7.5 M between the IDS gene and the telomere, based on the contents of 110 probes (figure 2). Overlaps have been confirmed with Alu and L1 fingerprinting, and the orders of markers in common is essentially completely concordant between the maps of abs. 26 and 89. The map has been further defined by the assembly of 57 contigs of cosmid clones which all together cover 7 of the estimated 9 Mb of DNA from FMR1/FRAXA to the Xq telomere. The largest contig extends 1.8 Mb centromeric to the GABRA locus, with 1.4 Mb in the DXS52-F8 region including two 600 kb contigs around G6PD and L1CAM. Additional contigs of cosmids from another library have been developed by Nelson et al. in regions that include the G6PD-color vision and ALD-V2R intervals. These regions include zones poorly cloned in YACs.

In a very interesting cloning effort based on the comparative mapping of mouse and human markers in the region, Pragliola and Herman (abs. 60) worked with the other groups to assemble YAC material across a gap between GABRA3 and DXS52. Four YACs span about 600 kb in the region, with the map starting from GABRA3 and DXS1104. In collaboration with Maestrini et al. (abs. 79), the same group has continued comparative analysis of mouse and human DNA (Angel et al., 1993) in the color vision-G6PD interval, with the determination of a consistent order of a number of markers in the two species. These are further examples of what can be expected from the astute use of syntenic equivalence.

Xq27.1-q28 has been assembled in a contig of 12 Mb, updated from CCM93 by Zucchi, Mumm et al., and now fitted with 120 STSs in 265 YACs. The region is adjacent to the centromeric 8.5 Mb contig reported earlier by Little et al. and also mapped in part by Cole et al. (see Schlessinger et al., 1993). The map of the entire region has been further verified by Alu and L1 fingerprinting and 353 hybridization probes.

Further centromeric, ~19 Mb of Xq24-q26.1 has now been assembled into 10 contigs containing 392 YACs ordered and oriented by a combination of probe content, 192 STSs, and three-color FISH analysis (abs. 59). Detailed mapping of 2 Mb in YACs, including the markers DXS6, DXS982, DXS739, and DXS100, was reported by Porta et al. (abs. 59) to cover essentially all of the smallest deletion known thus far in a patient with LYP (Skare et al., 1993; Wu et al., 1993). In general, the order of linkage markers in the physical map (see figure 1) and the genetic maps of CHLC and CEPH/Genethon are in agreement (apart from two markers which have not yet been precisely placed). The order of markers is generally concordant with inferences from other data. For example, linkage analysis in families with Lowe syndrome maps OCRL distal to DXS42 (abs. 58). Some discrepancies remain, however; for example, somatic cell hybrid panel mapping gives an order of DXS424 and DXS425 reversed from the one shown in the map. Such discrepancies may result from the occurrence of some markers at more than one chromosomal location and remain to be resolved.

The integration of linkage map information provides a critical test for consistency of both types of mapping results. In the portion that is most complete, from Xq26-qter, where marker order on the physical map is absolute, the order of markers in the physical map is concordant with linkage mapping (abs. 53 and unpublished observations). This encourages the expectation that discrepancies in Xq24-q25 will be resolved as the maps are further developed.

Gene finding has continued to be based largely on region-specific searches, influenced both by disease gene hunts and by the relative gene richness of some regions. Direct selection and CpG island-driven analyses continue to predominate, but increasingly are supplemented or complemented by direct sequencing to define genes and their locations.

The most extensive efforts have continued to identify cDNAs and genes that map to Xq28. Much of the work extends the studies of the groups of Poustka and Toniolo (see CCM93 report and Bione et al., 1993; Sedlacek et al., 1993). In efforts based on the recovery of cDNAs, a region-specific cDNA library has been organized (abs. 88), and 30 genes have been placed in the region from DXS304 to the telomere. In an extension of this effort, 500 cDNA candidates have been sequenced from both ends, with the recovery of more than 30 transcripts including a number of novel ones which are being mapped further (abs. 87). In the efforts from several groups, one species mapping upstream of the GABRA3 locus has been sequenced (abs. 7), and another mapping between GABRA3 and DXS52 (abs. 60) shows high homology with the beta-4 subunit of the chicken GABRAA receptor.

More specific efforts have continued with the further development of transcriptional maps around the L1CAM and G6PD regions (abs. 79 and 87) in the high GC subtelomeric region (Pilia et al., 1993; see also Willard et al., 1994). Since little specific sequence information is available for many of them, it is difficult to assess how many unique genes have been found; but for example, in an extension of the gene census given at CCM93, 19 genes and CpG islands have been identified between the RCP/GCP locus and G6PD, and at least 10 in the L1CAM region (abs. 79). One of the genes in the region is XAP-4, a rab GDP-dissociation inhibitor (abs. 90); another is a gene of ubiquitous expression adjacent to ALD (Mosser et al., 1994). Nelson et al. (abs. 56) have mapped a CCG repeat, two ESTSs (one overlapping XAP-3 of Sedlacek et al. (1993)), several novel genes, and a previously known gene (HCF1) to the zone. HCF1 was also found in the cDNA selection library of Korn et al. (abs. 88).

Further analyses of some of the genes in the region involved in inherited diseases have correlated mutational

changes with pathology (for example, for ALD, abs. 43, Sarde et al., 1994; for the type2 vasopressin receptor gene responsible for nephrogenic diabetes insipidus, Frattini et al, 1993; Faust et al., 1993; Knoers et al., 1993). In addition, the localization of several disease genes has been recently refined, including MTM1 myotubular myopathy between DXS304 and DXS305 (Dahl et al., 1994); BTHS Barth syndrome between DXS374(DXS305) and DXS52 (Ades et al., 1993); and the familial form of incontinentia pigmenti (IP2) distal to F8 (Smahi et al., 1994; Gorski and Burright, 1993). The linkage of dyskeratosis congenita to DXS52 was reaffirmed in studies of three additional families (Arngrimsson et al., 1993). For X-linked hydrocephalus, on the other hand, where an additional report (Jouet et al., 1993) confirmed the L1 defect previously shown (see CCM93 report and abs. 66), evidence has been obtained for a possible second locus closely linked to FRAXA (Strain et al., 1994). No genes have yet been reported in the Xq/Yq pseudoautosomal region, but a possible locus implicated in the detemination of sexual preference (Hamer et al., 1993) may map there.

Comparable methods have identified some genes in Xq27 (abs. 7, 80), including a cDNA, Xib1, mapped between DXS369 and DXS296, which is highly conserved and shows differential expression in embryonic tissues (abs. 7). The studies of the FMR1 gene region have continued with further studies of the methylation of the trinucleotide repeat region (Hornstra et al., 1993).

Several disease genes were further localized in Xq26-q27. They include the Borjeson-Forssman-Lehmann syndrome (abs. 45), for which the SOX3 gene, related to SRY and mapping to Xq26-q27, has been suggested as a candidate gene (Stevanovic et al., 1993). The Simpson-Golabi-Behmel gene has also been linked to Xq26 (abs. 57, Xuan et al., 1994; Orth et al., 1994), as has a nonspecific X-linked mental-retardation gene (Charlton et al., 1994) of unknown relation to others reported in the region.

Initial studies of Xq24-q26.1 have localized a number of cDNAs and ESTs, including some of those reported at the XCW4 and CCM93 (Parrish and Nelson, 1993; Mazzarella and Srivastava, 1994). The ANT2 ADP/ATP translocase gene was mapped in YACs 1 Mb distal to DXS425 in Xq25 (abs. 61); the CD40L ligand gene further localized 1 Mb distal to DXS144E (Pilia et al., 1994), and ZNF75 placed 1 Mb telomeric of HPRT (Villa et al., 1993). The CD40L ligand gene has continued to be the object of intensive further structural studies (Aruffo et al., 1993; Belmont et al., 1993; Fuleihan et al., 1993a,b; Villa et al., 1993).

Two CpG islands and one corresponding cDNA were localized in the candidate region for LYP in Xq25-q26.1 (abs. 59). These add to the groups of CpG islands previously reported to lie in the region (see CCM93 report and above). Other disease genes in the region include those for the thoraco-abdominal syndrome (Parvari et al., 1994) and familial situs abnormalities (Casey et al., 1993).

Sequencing projects

Complementary long-range sequencing and relevant technology development has taken off in Xq27.3-qter, in accord with a division of labor agreed on for the report from XCW4 (Schlessinger et al., 1993). The sequencing groups which had agreed to undertake significant pilot projects have all achieved their goals, using random shotgun sequencing of cosmids (figure 2).

In the most centromeric region currently under study, Andersson et al. (abs. 3) reported on improved methods for subcloning of larger clones into M13 sequencing substrates and on a use of directed PCR to clone an otherwise unrecovered fragment. These methods were employed in sequencing cosmids containing 170 kb around the FRAXA locus; a region near the FRAXE site containing highly likely candidates for exons; the IDS gene and part of the TH4 cDNA; the DXS455 locus; and the AGMX locus in Xq22 (abs. 32).

Further distal, the high GC/gene-rich region between L1CAM and G6PD has been studied in several initiatives. The efforts of Rosenthal in conjunction with the groups of Poustka in Heidelerg and Bentley at the Sanger Centre have analyzed three cosmids in the L1CAM-RCP/GCP interval by shotgun sequencing, determining the structures of the L1CAM and HCF1 genes, delimiting the position of the vasopressin receptor V2 gene, and localizing precisely the position of the renin-binding protein (abs. 66, and for the RENBP, cf. van den Ouweland et al., 1994). The Sanger Centre activities (abs. 11) have completely sequenced a further 109 kb section moving centromeric to the RCP/GCP locus in four overlapping cosmids. The analysis of the region has thus far revealed both a new member of the transketolase family and a member of the green opsin cluster with a CpG island at its 5' end.

On the telomeric side of the RCP/GCP locus, 200 kb of DNA has been sequenced and partially analyzed by the groups of Chen and D'Urso (abs. 15), with the assembly and verification of the sequence still ongoing. Three possible genes were detected by computer-aided predictions in 33 kb centromeric to G6PD, two of which have been confirmed by the verification of cDNAs authentically encoded by those loci. One of them had been independently isolated by direct selection methods in the groups of Poustka and Toniolo [2-19 of Bione et al., 1993 and likely XAP-7 of Sedlacek et al., 1993]; the other is previously unreported. Incomplete analysis of the rest of the region has been done first with gene-finding software and then by comparison with genes and ESTs in databases. Thus far, predictions agree with detected known genes for FLN, QM, and the XAP-1 to XAP-5 cDNAs of Sedlacek et al. (1993). Thus, computer-aided gene searches are already supplementing direct searches for cDNAs, and in turn can provide additional candidates to be tested for confirmation by direct gene-finding techniques.

In the coming year, the groups will continue with the extension of sequencing to cover the initially targeted regions, and with projected additional efforts that include sequencing between IDS and DXS304 (Sanger Centre), telomeric of G6PD (D'Urso), and centromeric of HPRT in Xq26 and in the region of EDA in Xq12-q13.1 (Chen).

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Figure Legends

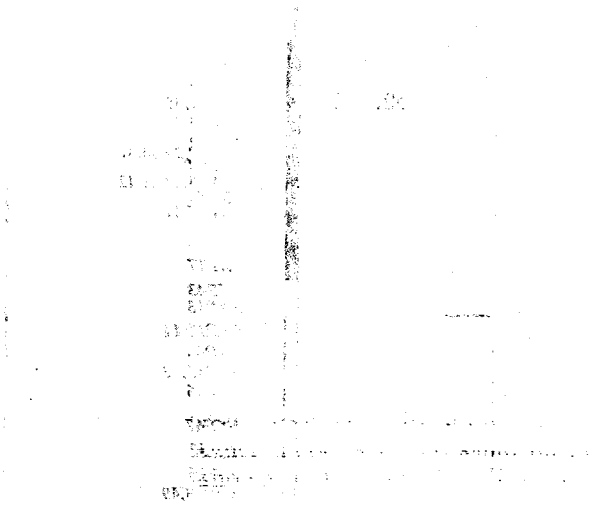
Fig 1 Consensus map of the X chromosome. This map represents a compilation of information regarding physical mapping of the chromosome from a variety of sources, as interpreted by the X chromosome editors and by the participants at the workshop. The map is an update of a similar map published as part of the CCM93 proceedings (Willard et al., 1994). Anonymous markers, genes, and breakpoints are indicated in order along the chromosome relative to a scale of 160 units -- roughly equivalent to megabases -- approximating the distance from pter to qter. The figure is dividing into ~20 Mb segments. Small duplications at the limits of each section have been introduced graphically (i.e. at the bottom of one section and the top of the next) to facilitate interpretation of the map.

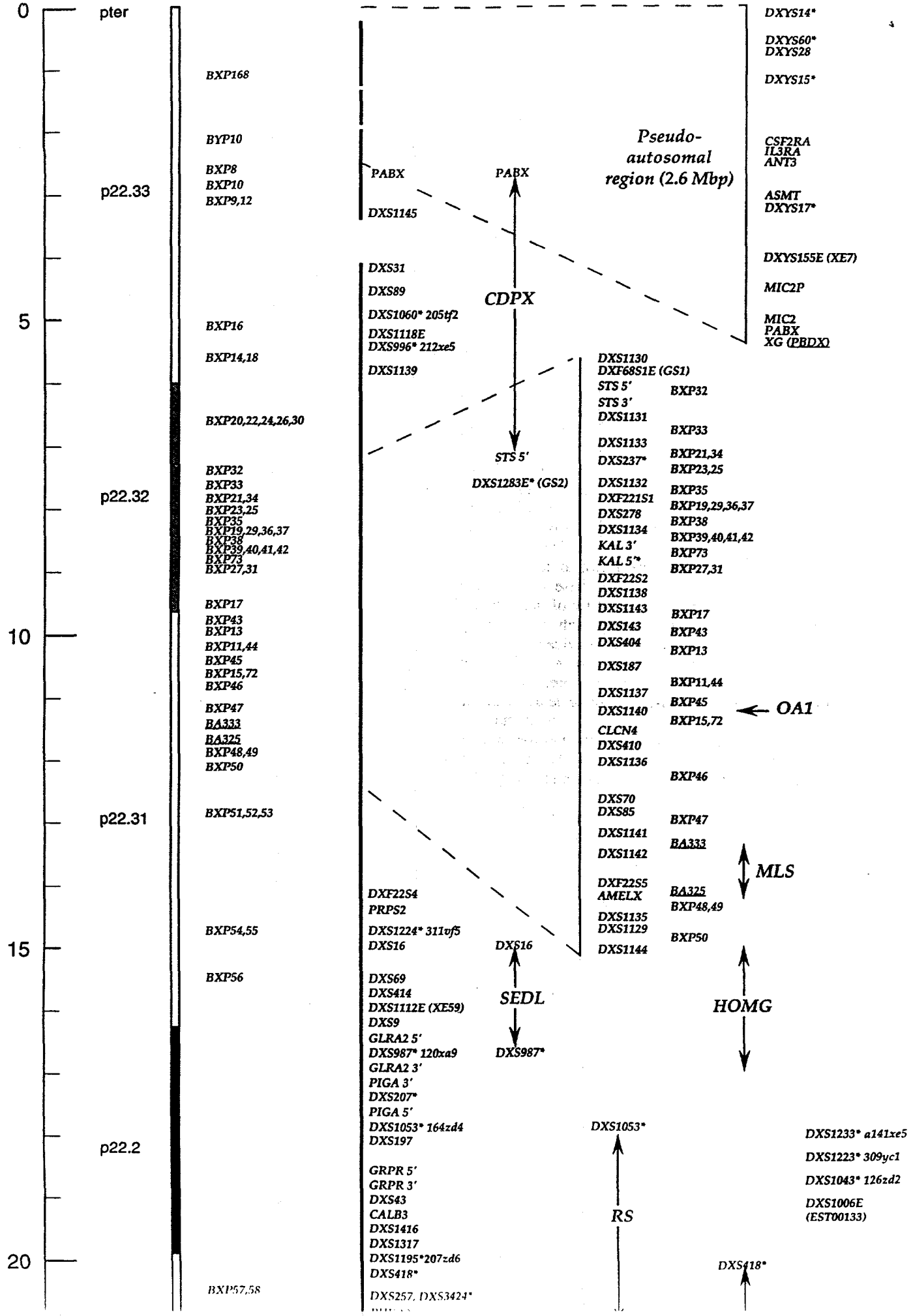
The approximate location of cytogenetic bands is also indicated. Loci with highly informative microsatellite repeats are indicated by asterisks; full information on the polymorphisms can be obtained from GDB. YAC contigs are indicated by vertical bars; those closest to the chromosome are drawn to scale. Some contigs are expanded to show detail; these are indicated by dashed lines. Support for the order of map objects shown on the YAC contigs is very high, representing consensus among two or more lines of evidence.

DNA segments and genes shown to the left of the YAC contigs are ordered relative to breakpoints, but usually do not have a consensus order relative to the other markers in the same interval, or with markers shown in YAC contigs. Breakpoints in some regions are indicated twice, once next to the chromosome to maintain the linear order and again in the relevant YAC contigs.

Phenotypes for which genes have not yet been identified are indicated in large type, often on double-headed arrows to indicate the region to which the gene has been localized, usually by linkage analysis. Horizontal arrowheads are used for phenotypes with very high probability locations between markers (as in the case of phenotypes associated with well-mapped X;autosome translocations, for example).

Objects to the extreme right of the figure have not been placed into the physical map with high confidence, but are deemed important and are therefore indicated with the expectation that they will be placed into the next version of the map by interested groups. A number of map objects are not represented in GDB (as of the date of the workshop); these are highlighted by underlining and are designated with various "private" nomenclature.

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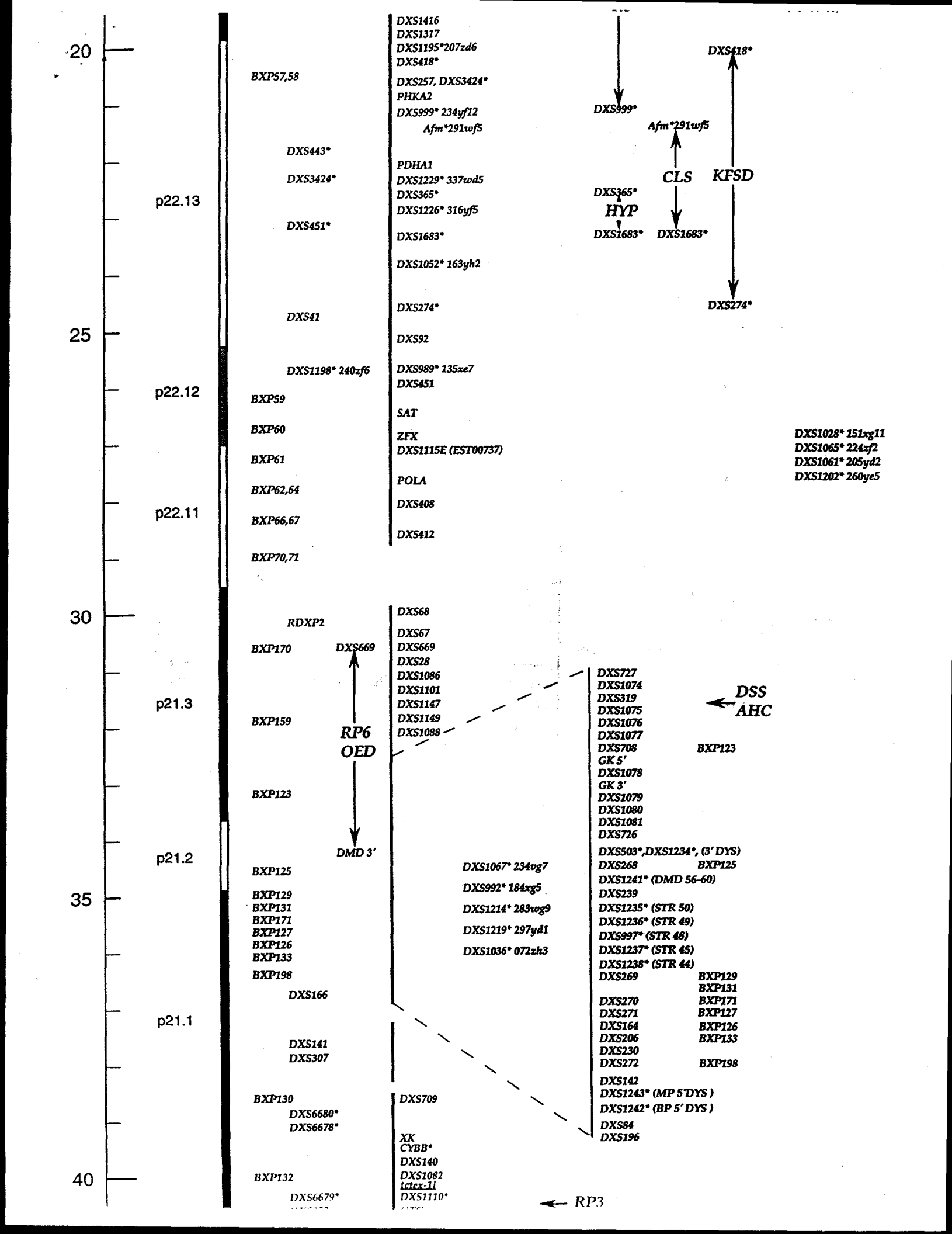
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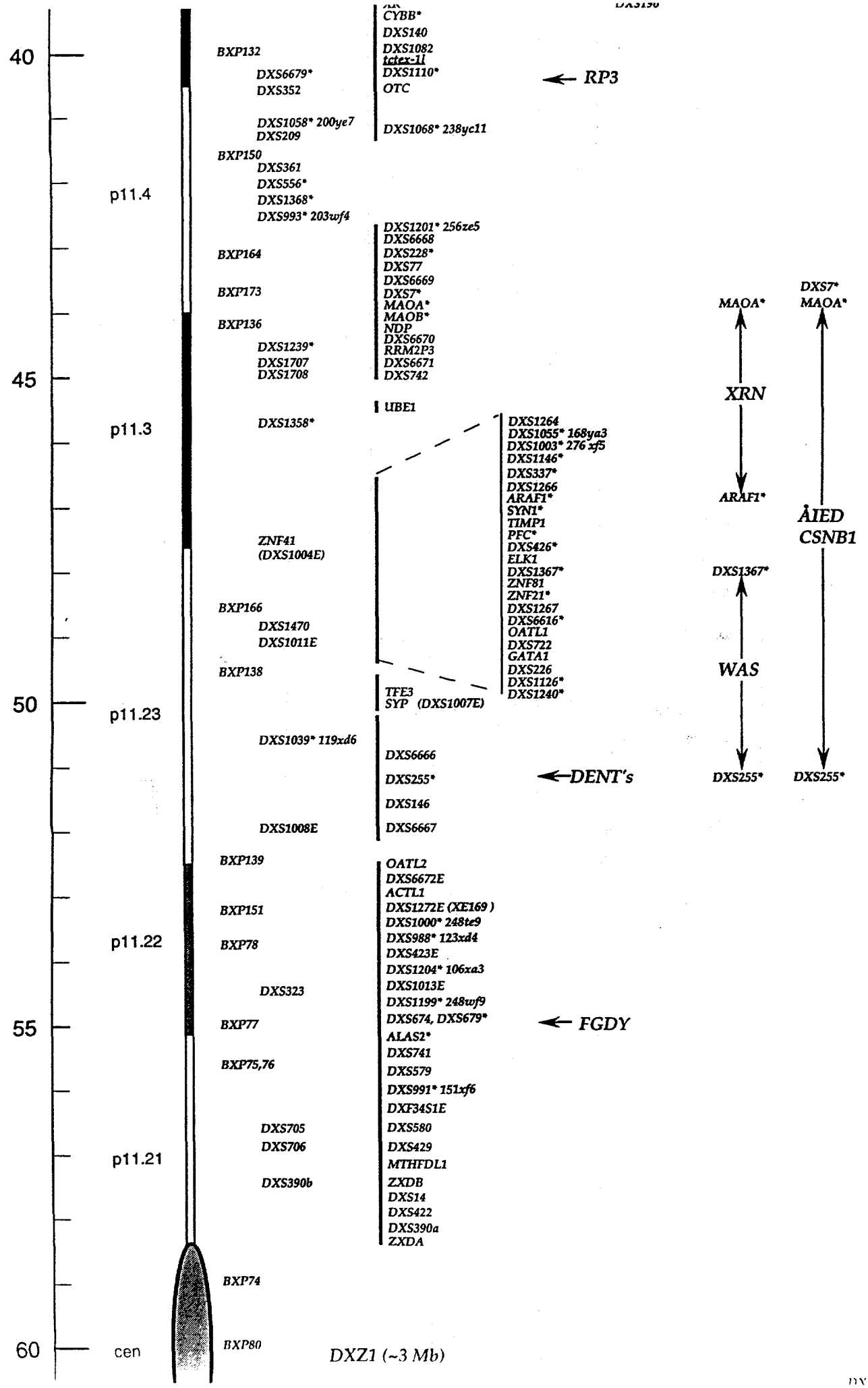
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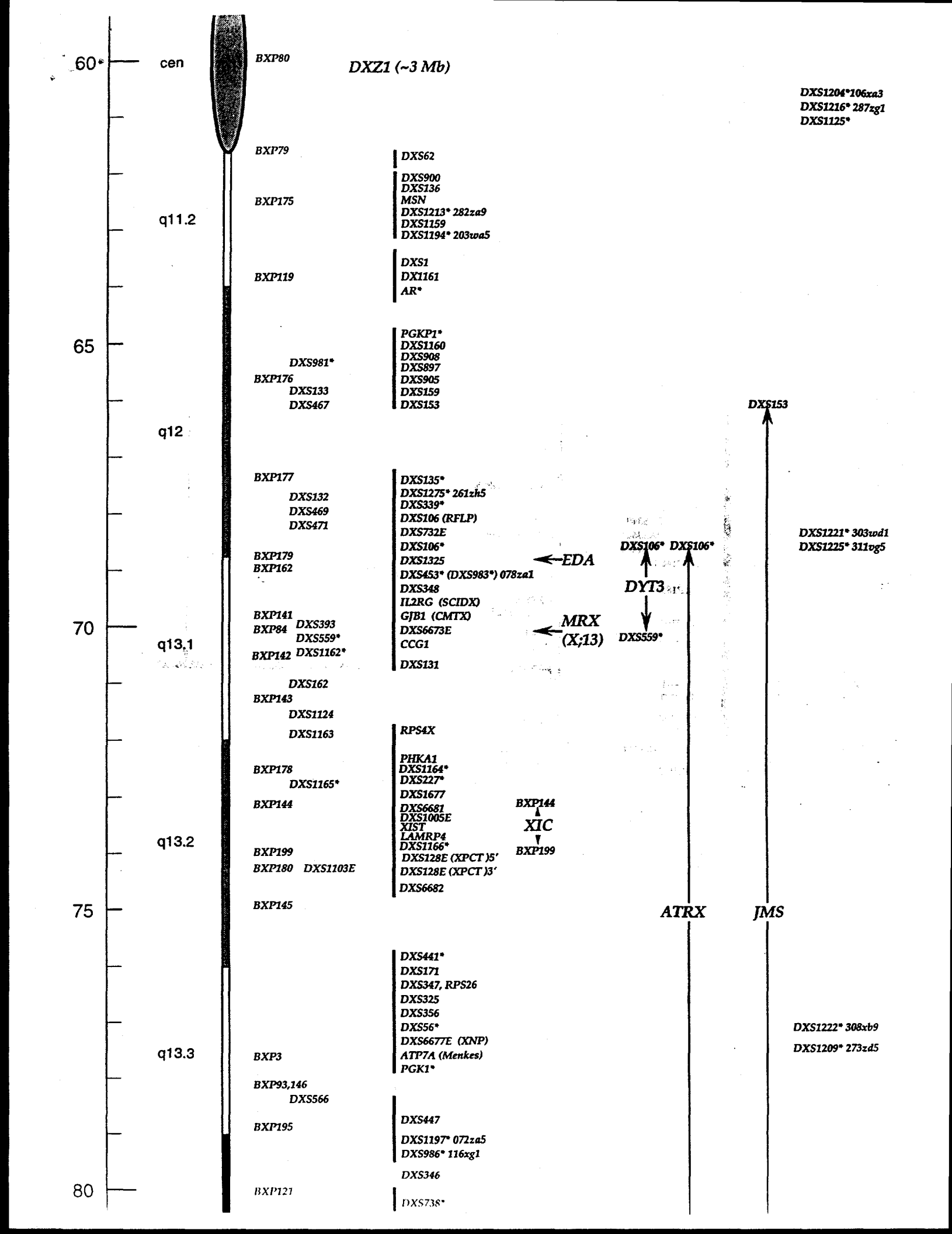
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DXS453* (DXS983*) 078za1
DYT3
DXS348
IL2RG (SCIDX)
BXP141
GJB1 (CMTX)
MRX
70
BXP84
DXS393
DXS6673E
(X;13)
DXS559*
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q13.1
DXS559*
CCG1
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RPS4X
PHKA1
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DXS1164*
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DXS1677
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DXS1005E
XIC
XIST
q13.2
LAMRP4
DXS1166*
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BXP199
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BXP180
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75
BXP145
ATRX
JMS
DXS441*
DXS171
DXS347, RPS26
DXS325
DXS356
DXS56*
DXS1222* 308xb9
DXS6677E (XNP)
q13.3
DXS1209* 273zd5
BXP3
ATP7A (Menkes)
PGK1*
BXP93,146
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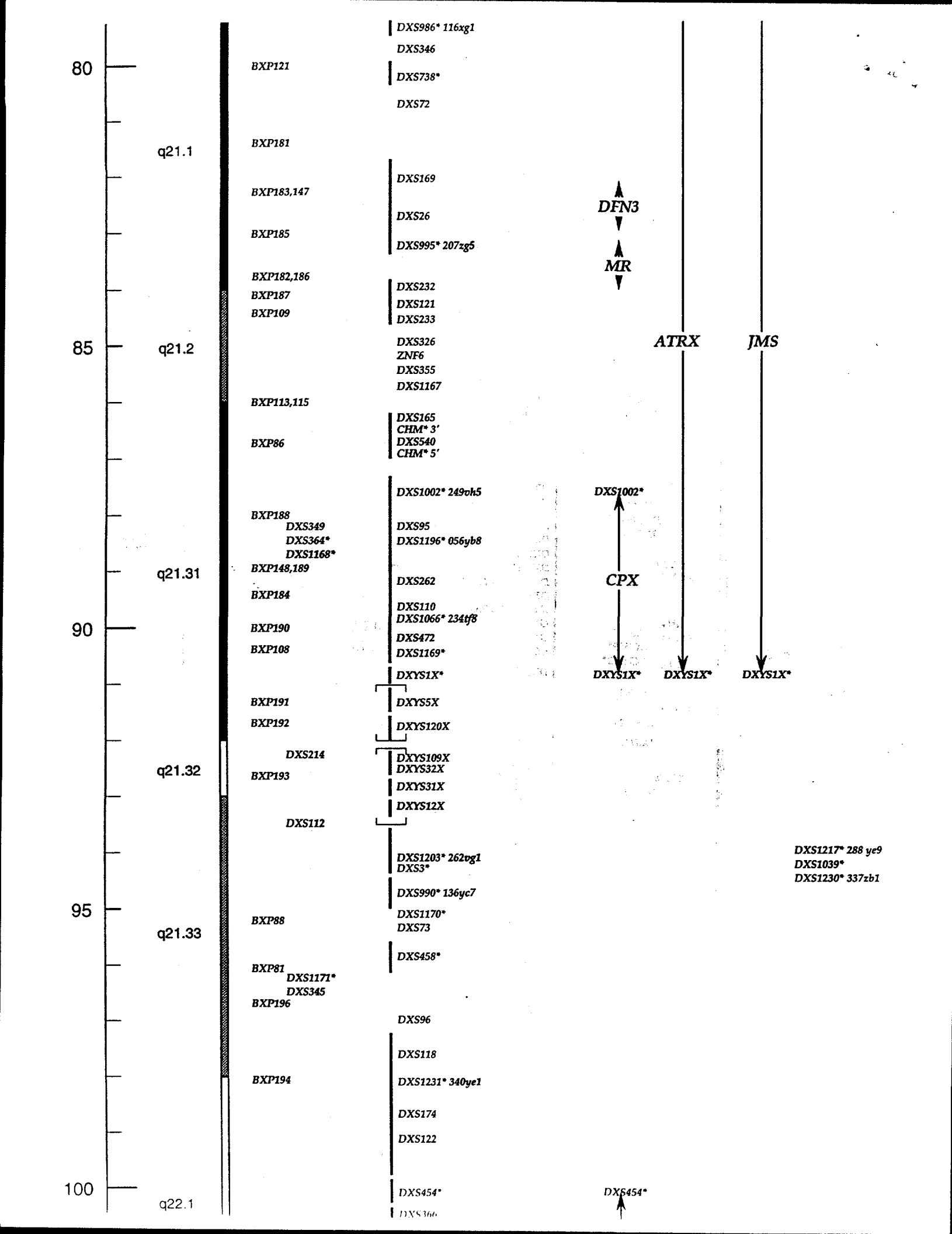
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DXS72
DXS169
DXS26
DXS995* 207zg5
DXS232
DXS121
DXS233
DXS326
ZNF6
DXS355
DXS1167
DXS165
CHM* 3'
DXS540
CHM* 5'
DXS1002* 249oh5
DXS95
DXS1196* 056yb8
DXS262
DXS110
DXS1066* 234tf8
DXS472
DXS1169*
DXYS1X*
DXYS5X
DXYS120X
DXYS109X
DXYS32X
DXYS31X
DXYS12X
DXS1203* 262vg1
DXS3*
DXS990* 136yc7
DXS1170*
DXS73
DXS458*
DXS96
DXS118
DXS1231* 340ye1
DXS174
DXS122
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DFN3
MR
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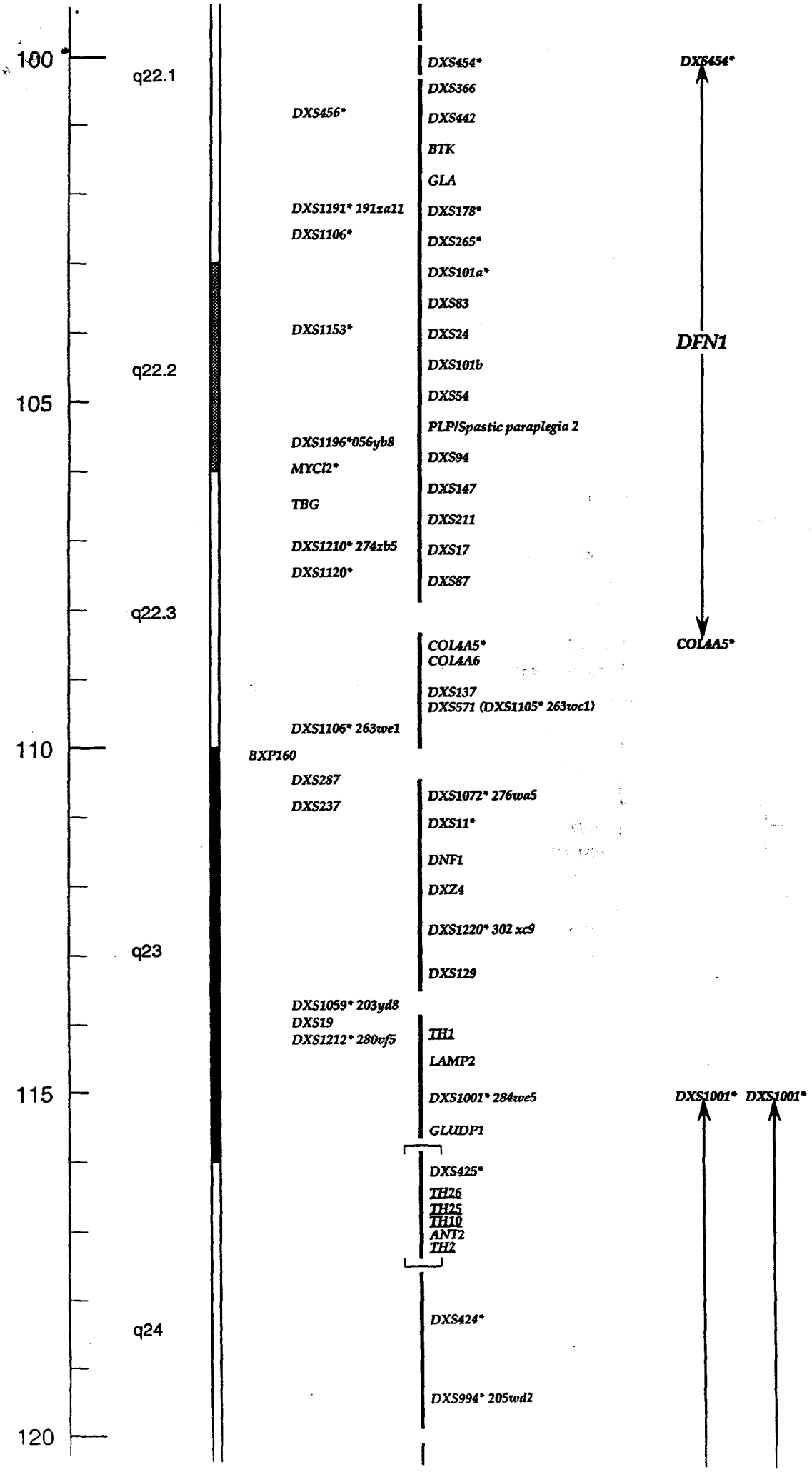
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DXS101a*
DXS83
DXS1153*
DXS24
DFN1
q22.2
DXS101b
105
DXS54
PLP/Spastic paraplegia 2
DXS1196*056yb8
DXS94
MYCI2*
DXS147
TBG
DXS211
DXS1210* 274zb5
DXS17
DXS1120*
DXS87
q22.3
COL4A5*
COL4A6
DXS137
DXS571 (DXS1105* 263wc1)
DXS1106* 263we1
110
BXP160
DXS287
DXS237
DXS1072* 276wa5
DXS11*
DNF1
DXZ4
DXS1220* 302 xc9
q23
DXS129
DXS1059* 203yd8
DXS19
DXS1212* 280wf5
TH1
LAMP2
115
DXS1001* 284we5
GLUDP1
DXS425*
TH26
TH25
TH10
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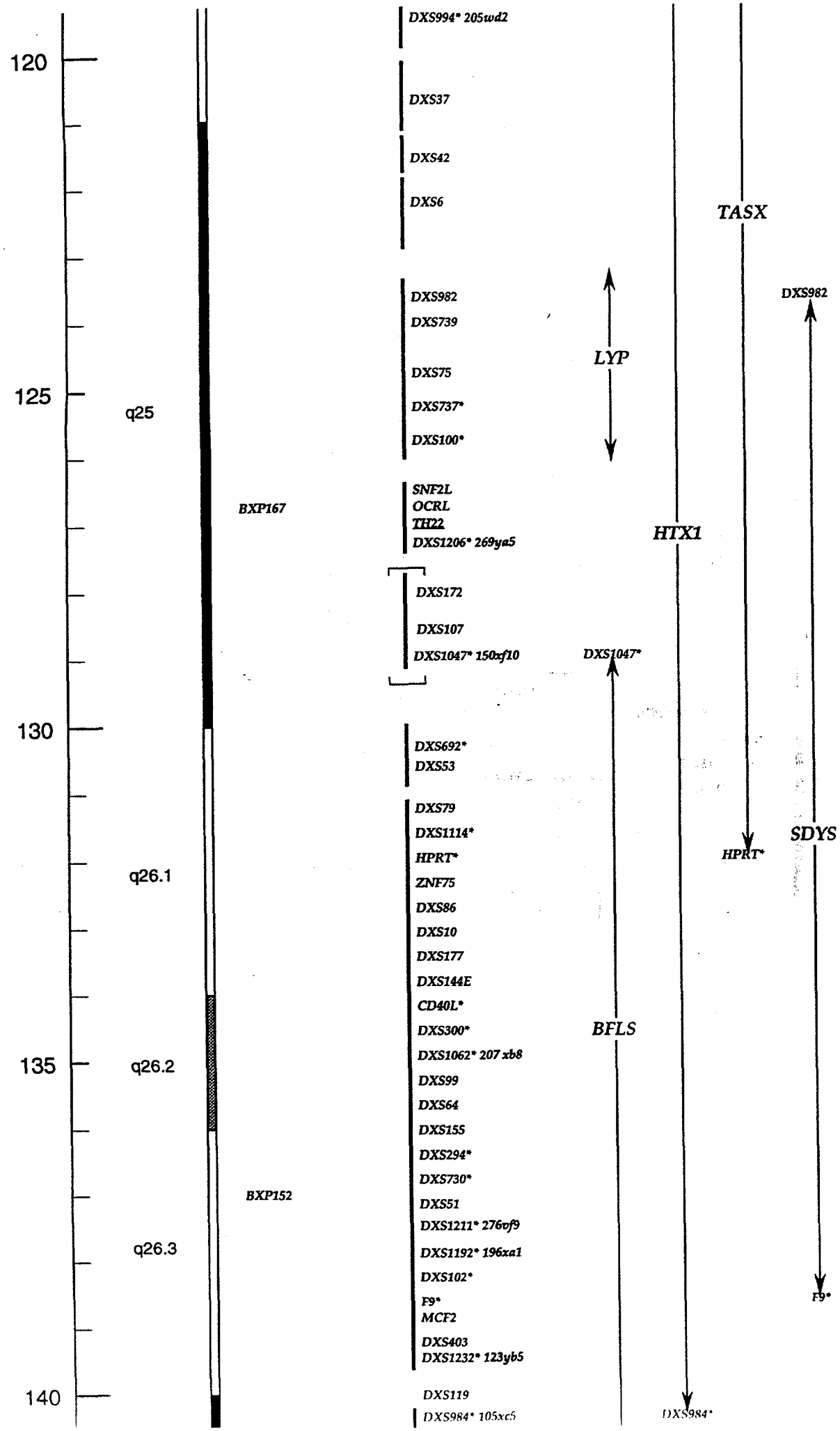
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BXP152
DXS994* 205wd2
DXS37
DXS42
DXS6
DXS982
DXS739
DXS75
DXS737*
DXS100*
SNF2L
OCRL
TH22
DXS1206* 269ya5
DXS172
DXS107
DXS1047* 150xf10
DXS692*
DXS53
DXS79
DXS1114*
HPRT*
ZNF75
DXS86
DXS10
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DXS144E
CD40L*
DXS300*
DXS1062* 207xb8
DXS99
DXS64
DXS155
DXS294*
DXS730*
DXS51
DXS1211* 276vf9
DXS1192* 196xa1
DXS102*
F9*
MCF2
DXS403
DXS1232* 123yb5
DXS119
DXS984* 105xc5
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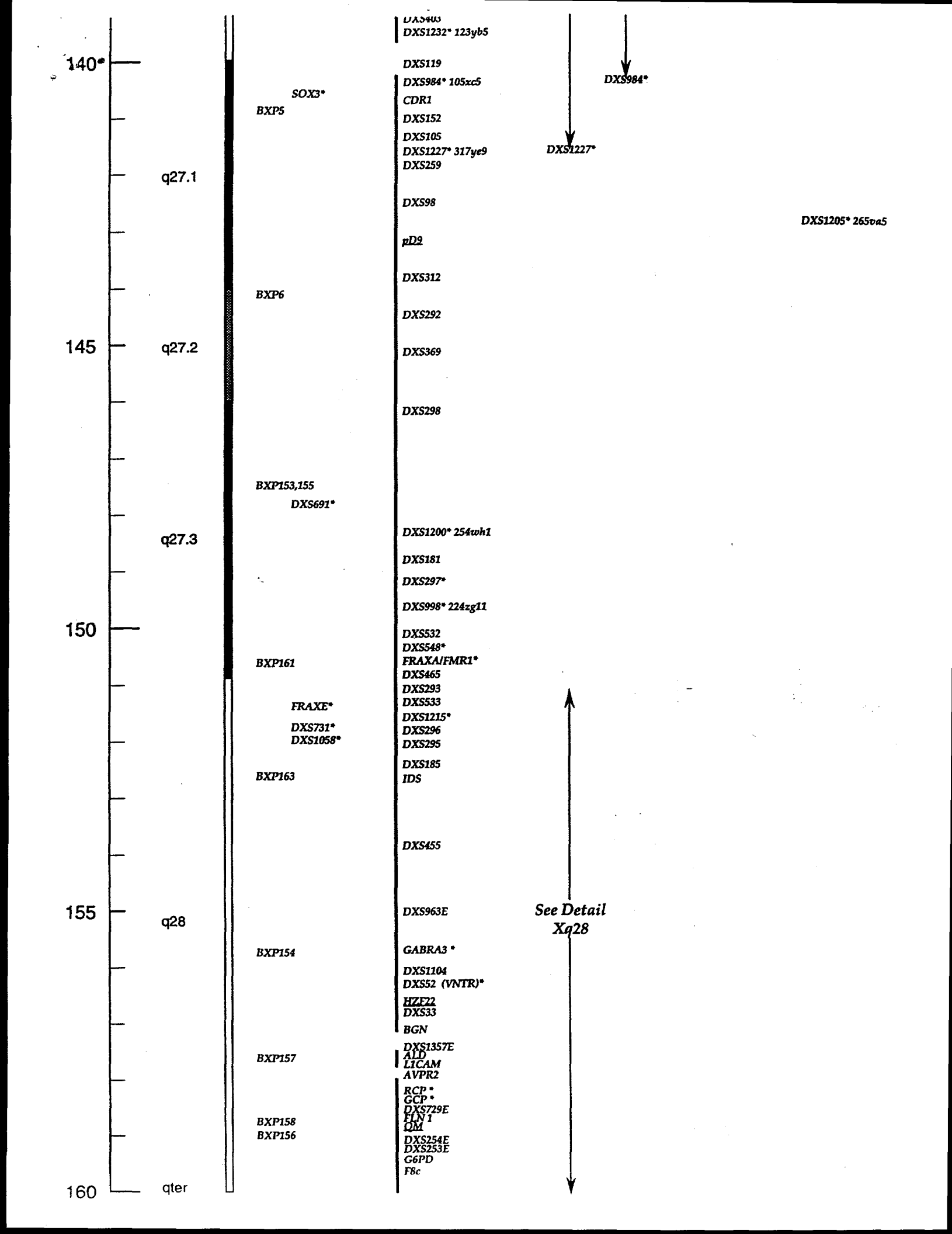
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q27.1
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qter
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DXS691*
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FRAXE*
DXS731*
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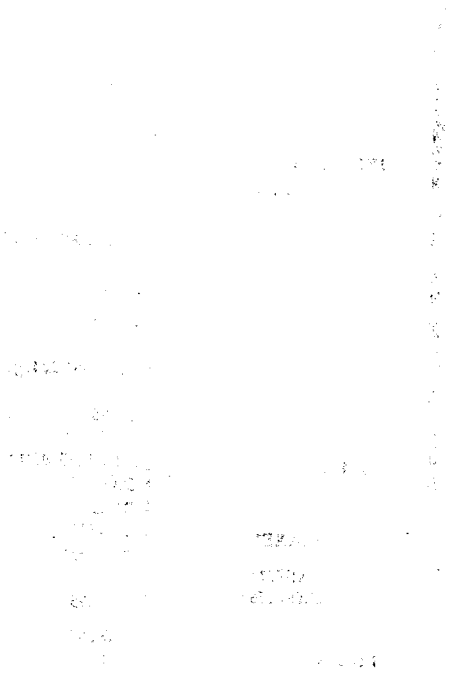
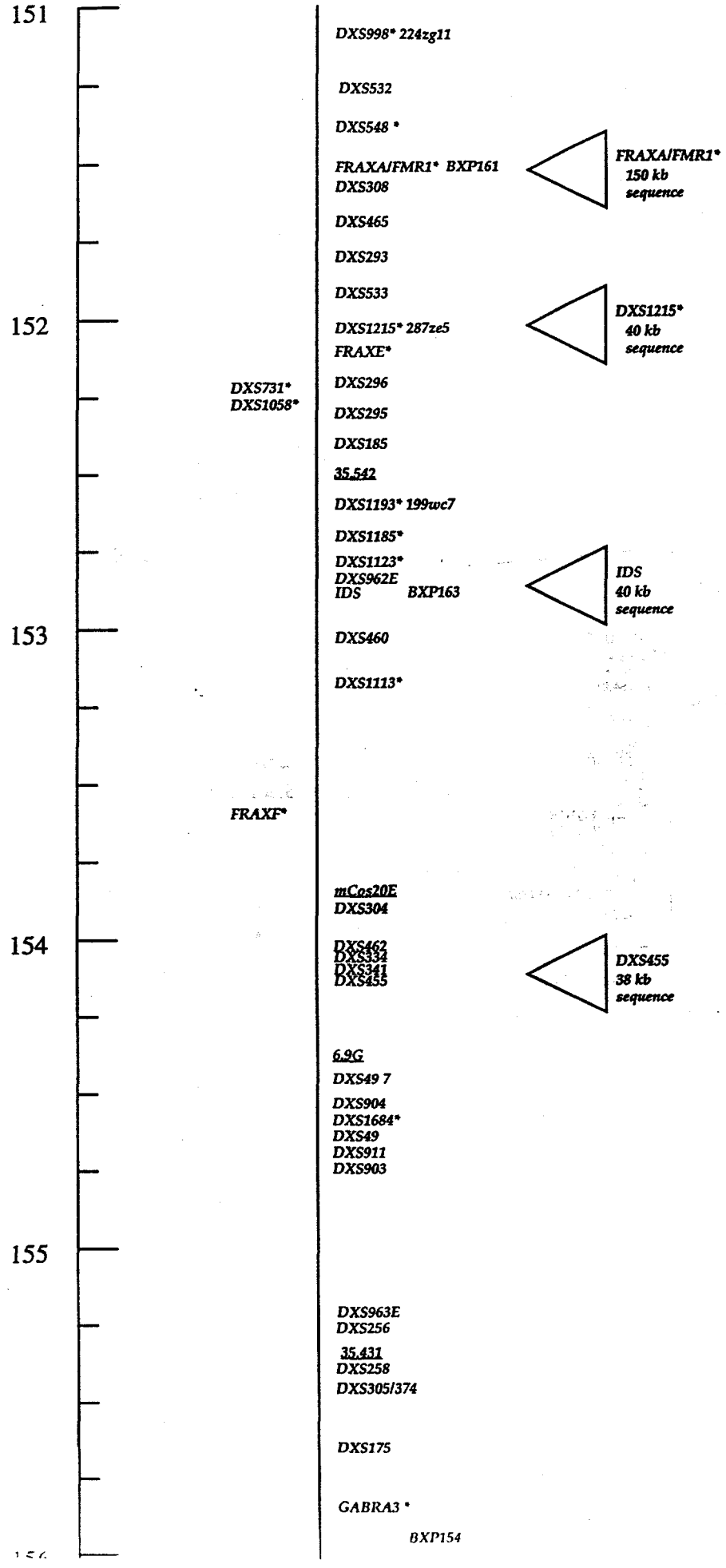
BXP163
BXP154
BXP157
BXP158
BXP156
DXS1232* 123yb5
DXS119
DXS984* 105xc5
CDR1
DXS152
DXS105
DXS1227* 317ye9
DXS259
DXS98
pD2
DXS312
DXS292
DXS369
DXS298
DXS1200* 254wh1
DXS181
DXS297*
DXS998* 224zg11
DXS532
DXS548*
FRAXA/FMR1*
DXS465
DXS293
DXS533
DXS1215*
DXS296
DXS295
DXS185
IDS
DXS455
DXS963E
GABRA3 *
DXS1104
DXS52 (VNTR)*
HZF22
DXS33
BGN
DXS1357E
ALD
L1CAM
AVPR2
RCP *
GCP *
DXS729E
FLN 1
QM
DXS254E
DXS253E
G6PD
F8c
DXS984*
DXS1227*
DXS1205* 265va5
See Detail
Xq28

Figure Legends

Fig 2 Expanded map of Xq28 (positions 151-160). Conventions are as in figure 1. In addition, triangles are used to indicate regions of signficant sequence data. A number of novel genes are indicated in the distal portion of the map; those with more than one symbol are indicated as "a/b".



Xq28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DXS308
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DXS293
DXS533
DXS1215* 287ze5
FRAXE*
DXS296
DXS295
DXS185
35.542
DXS1193* 199wc7
DXS1185*
DXS1123*
DXS962E
IDS BXP163
DXS460
DXS1113*
mCos20E
DXS304
DXS462
DXS334
DXS341
DXS455
6.9G
DXS49 7
DXS904
DXS1684*
DXS49
DXS911
DXS903
DXS963E
DXS256
35.431
DXS258
DXS305/374
DXS175
GABRA3 *
BXP154
DXS731*
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FRAXF*
FRAXA/FMR1*
150 kb
sequence
DXS1215*
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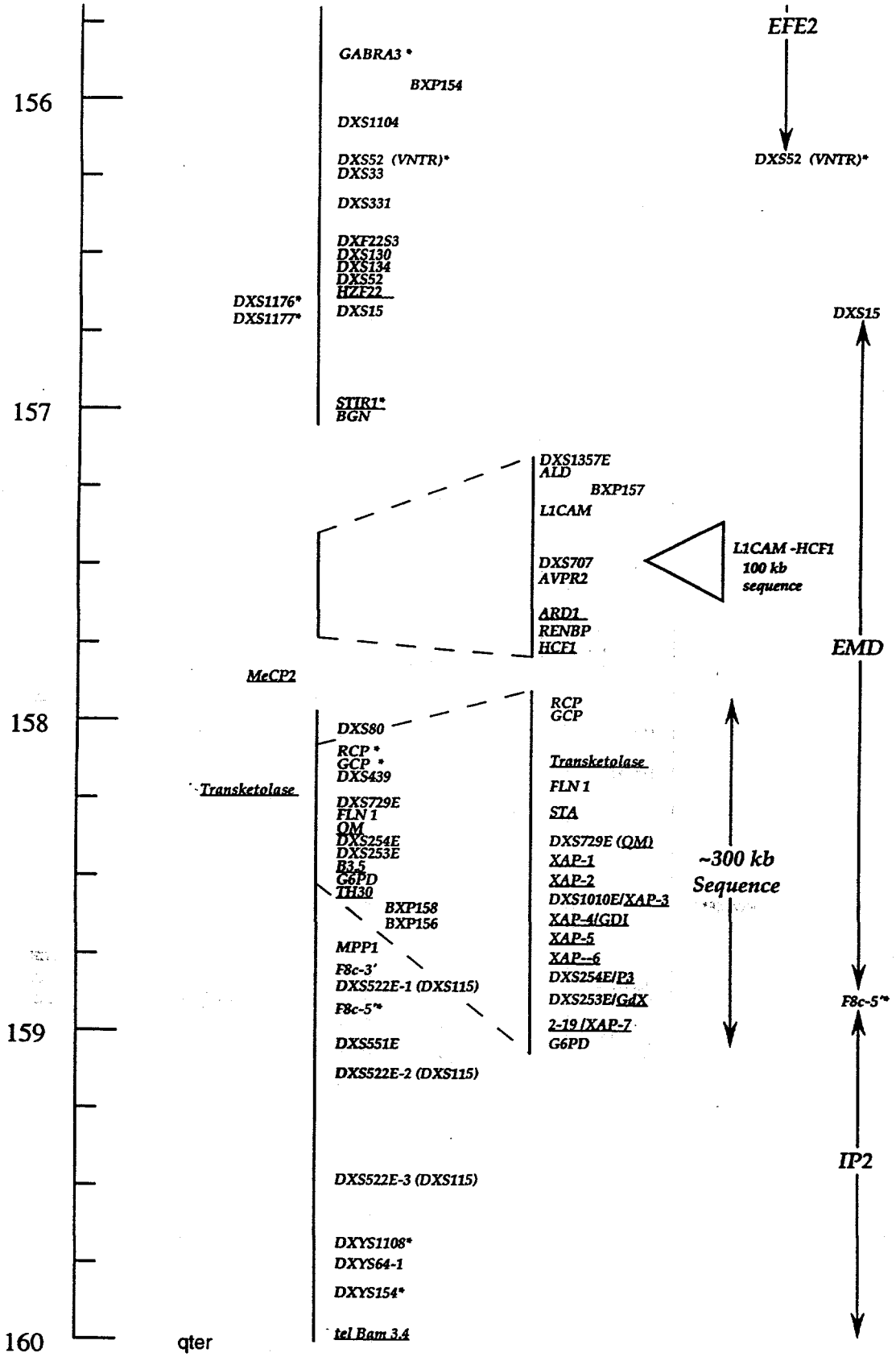
156
157
158
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160
qter
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DXS331
DXF22S3
DXS130
DXS134
DXS52
HZF22
DXS1176*
DXS1177*
DXS15
STIR1*
BGN
DXS1357E
ALD
BXP157
L1CAM
DXS707
AVPR2
ARD1
RENBP
HCF1
MeCP2
DXS80
RCP *
GCP *
DXS439
Transketolase
DXS729E
FLN 1
QM
DXS254E
DXS253E
B3.5
G6PD
TH30
BXP158
BXP156
MPP1
F8c-3'
DXS522E-1 (DXS115)
F8c-5'*
DXS551E
DXS522E-2 (DXS115)
DXS522E-3 (DXS115)
DXYS1108*
DXYS64-1
DXYS154*
tel Bam 3.4
RCP
GCP
Transketolase
FLN 1
STA
DXS729E (QM)
XAP-1
XAP-2
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XAP-5
XAP--6
DXS254E/P3
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2-19 /XAP-7
G6PD
~300 kb
Sequence
L1CAM -HCF1
100 kb
sequence
EFE2
DXS52 (VNTR)*
DXS15
EMD
F8c-5'*
IP2

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