Cytogenet Cell Genet 90:1–12 (2000)

Cytogenetics and Cell Genetics

Report of the

Third International Workshop on Human Chromosome 10 Mapping and Sequencing 1999

Held on September 30 to October 2, 1999
at The Sanger Centre, Wellcome Trust Genome Campus,
Hinxton, Cambridge, UK

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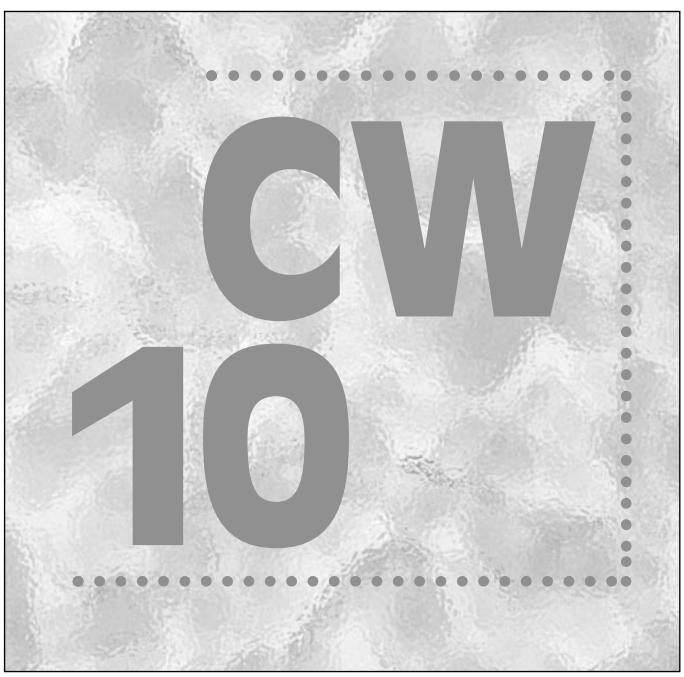

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Accepted for publication:
June 25, 2000

Report of the third international workshop on human chromosome 10 mapping and sequencing 1999

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The third international workshop on human chromosome 10 mapping was held in Hinxton, U.K. from the 30th September to 2nd October 1999. The workshop took place at The Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge. The meeting was attended by 34 participants, from nine countries (Belgium, Finland, France, Germany, Greece, New Zealand, Portugal, UK, and the USA).

The major goals of the workshop were to assess the progress in the physical mapping and sequencing of chromosome 10 since the last workshop in March 1997, to review database resources on the web that provide this sort of information, and to discuss the progress that has been made in identifying the genetic cause of disorders linked to chromosome 10.

To date a total of 212 genes, 58 disorder loci, 13 pseudogenes and 3 putative genes have been described as mapping to chromosome 10 (Table 1). Table 2 shows the disease loci and genes mapped to chromosome 10 since the last workshop.

Table 1. Chromosome 10 genes and disorders (updated from GDB; as per 26 September 1999)

Genes	212 (166)[a]
Disorder loci	58 (37)
Pseudogenes	13 (13)
Putative genes	3

[a] The respective numbers reported in the 2nd International Workshop (March, 1997), are indicated in parenthesis.

Physical mapping and sequencing – Regional and whole chromosome projects

With most if not all of the key players present, the workshop offered a unique opportunity to assess progress in mapping and sequencing chromosome 10 as part of the Human Genome Project (HGP). French et al. (CIT:777932) reported their progress in constructing a sequence-ready map of the entire chromosome using BACs. This project started at the Sanger Centre in October 1998 and at the time of the workshop 2993 chromosome 10–specific STSs have been used to isolate 15,411 BAC clones (RPCI-11 BAC library). The RPCI-11 BAC library has been fingerprinted at the Genome Sequencing Center, Washington University School of Medicine, St Louis USA and a database of fingerprints is available at http://genome.wustl.edu/gsc/human/human_database.shtml. French reported that they assemble contigs using landmark and fingerprint data and that a total of 179 contigs (Fig. 1), representing 91 Mb, were used to select clones for sequencing. Moschonas reported their progress in building a sequence-ready map between D10S541 and D10S554 (Sarafidon et al., CIT:777927) and between D10S186 and qtel (Pasparaki et al., CIT:777944) in collaboration with the Sanger group. The contribution of the participating groups that focus on the positional cloning of disease loci, included: (i) the construction of an ~1-Mb PAC/BAC contig across the HDR-syndrome locus (Van Esch et al., CIT:777939), (ii) the construction of a contiguous 700-kb PAC contig across the DGS2 region (Lichtner et al., CIT:777940), (iii) the construction of an ~ 1.2-Mb BAC contig across the schizophrenia locus on 10p (Wildenauer et al., CIT: 777942), (iv) (Siebert et al., CIT:777945), and (v) the construction of an ~350-kb PAC/BAC across the infantile onset spinocerebellar ataxia locus

We thank the Wellcome Trust and the Genome Therapeutics Corporation for their financial support organizing the workshop.

Received 5 June 2000; manuscript accepted 25 June 2000.

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Table 2. Disease loci/genes mapped to chromosome 10 since the 2nd International Workshop (March, 1997)

Disease locus/gene	Symbol	Location	Reference
Hypoparathyroidism, sensorineural deafness, renal dysplasia, HDR syndrome	HDR[c]	10pter→p13	Hasegawa et al. (1997)
Schizophrenia locus	–	10p14→p11	Schwab et al. (1998) Straub et al. (1998) Wildenauer et al. (CIT:777942)
Interleukin-2 receptor, deficiency of α-chain	IL2RA	10p15→p14	Sharfe et al. (1997)
Glaucoma 1E, primary open angle, adult onset	GLC1E	10p15→p14	Sarfarazi et al. (1998)
Diabetes mellitus-10, insulin dependent	IDDM10	10p11→q11	Reed et al. (1997)
Obesity susceptibility	OB10[c]	10p	Hager et al. (1998)
Immunodeficiency disease, severe, combined, Athabascan Type 2	SCIDA	10p	Li et al. (1998)
Hemophagocytic lymphohistiocytosis familial, HPLH2	PRF1	10q21→q22	Dufourcq-Lagelouse et al. (1999) Stepp et al. (1999)
Spondyloepimetaphyseal dysplasia SEMD, Pakistani type	ATPSK2	10q23→q24	Haque et al. (1998)
Urofacial (Ochoa) syndrome	UFS	10q23→q24	Wang et al. (1997, 1999)
Hyperinsulinism-hyperammonemia syndrome, glutamate dehydrogenase	GLUD1	10q23.3	Stanley et al. (1998)
Bannayan-Zonana syndrome, polyposis, juvenile intestinal phosphatase and tensin homolog	PTEN[a]	10q23.3	Carethers et al. (1998) Olschwang et al. (1998)
Epilepsy partial[a]	EPT[b]	10q23.3→q24.1	Ottman et al. (1995)
Autosomal dominant lateral temporal epilepsy	–	10q23→q24	Pozza et al. (1999)
Spastic paraparesis with amyotrophy, cataracts and gastroesophageal reflux, spastic paraplegia-9	SPG9	10q23.3→q24.1	Seri et al. (1999)
Corneal dystrophy, Thiel-Behnke type	CDB2/CDTB	10q23→q24	Yee et al. (1997)
Dubin-Johnson syndrome, canalicular multispecific organic anion transporter	ABCC2	10q24	van Kuijck et al. (1997)
Tolbutamide poor metabolizer; Warfarin sensitivity	CYP2C9[a]	10q24	Sullivan-Klose et al. (1996)
Diabetes mellitus 17, insulin dependent	IDDM17	10q25	Verge et al. (1998)
Anterior segment mesenchymal dysgenesis and cataract; paired-like homeodomain transcription factor-3	PITX3	10q25	Semina et al. (1998)
Glioblastoma multiformae; Medulloblastoma; Deleted in malignant brain tumors 1	DMBT1	10q25.3→q26.1	Mollenhauer et al. (1997)
Endometrial carcinoma; deleted in endometrial carcinoma	DEC[c]	10q26	Peiffer-Schneider et al. (1998)
Saethre-Chotzen syndrome; fibroblast growth factor receptor-2	FGFR2[a]	10q26	Paznekas et al. (1998)
Leprosy susceptibility locus		10p	Tosh et al. (CIT:777937)

[a] Additional disease(s) associated with the gene.
[b] Refined map location suggested by GDB.
[c] Symbol according to the OMIM database.

(IOSCA) (Nikali et al., CIT: 777946). In addition, Thiesen (CIT: 777928) and Guy (CIT: 777929) reported the construction of sequence-ready contigs across the p and q arm pericentromeric regions of the chromosome, respectively. The spirit of collaboration was reflected by the fact that all of the above groups have kindly provided their contigs to the Sanger group for map integration prior to or soon after the workshop. Finally, Eccles (CIT:777930) reported on a discrepancy between the genetic map and a 1-Mb physical map of 10q24 that they constructed. Although the order of genes cen–PAX2–HOX11–NFKB2–GOT1–WNT8–qtel in the genetic map correlated well with that observed in the physical map it was in the reverse orientation. The human gene map (Deloukas et al., 1998) also reports GOT1 mapping centromeric of HOX11.

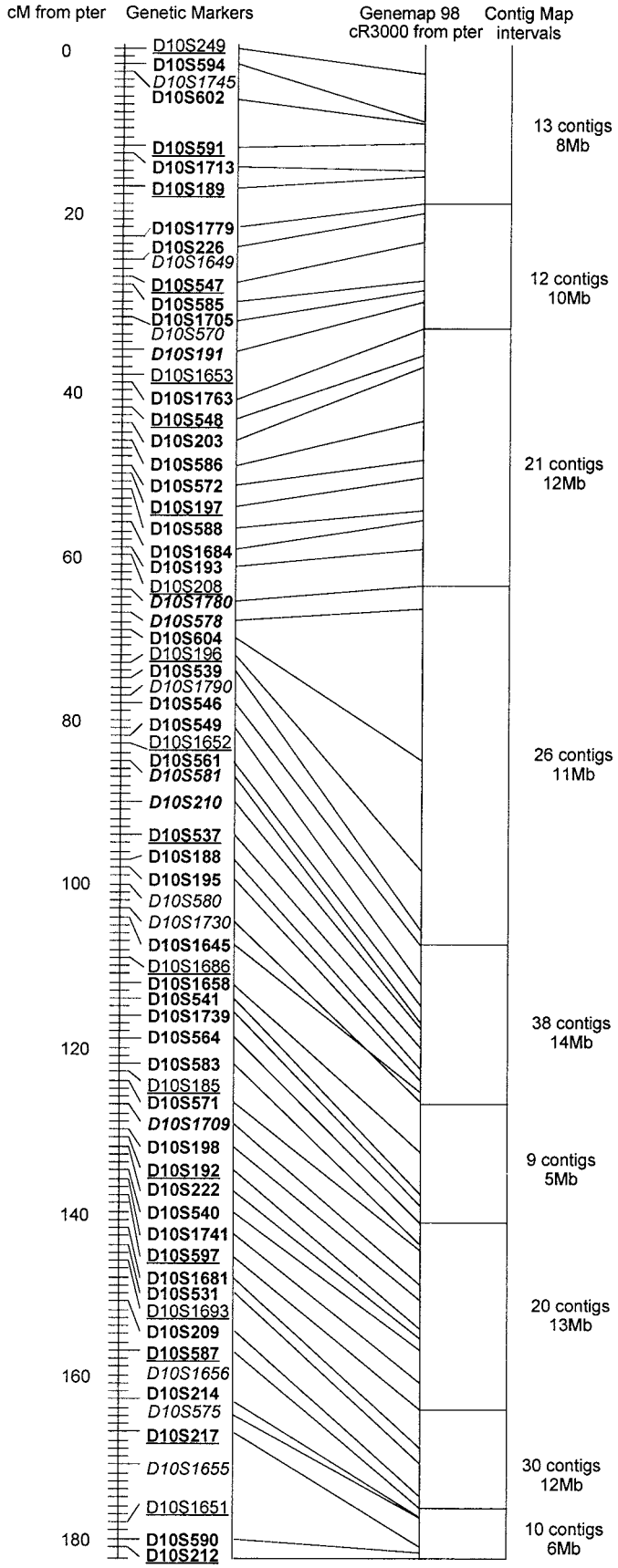
The sequencing targets of the HGP are to generate a draft sequence by spring 2000 and the finished contiguous sequence by 2003. The sequencing of chromosome 10 is being undertaken by both the Genome Therapeutics Corporation (GTC) (using NIH funds) and the Sanger Centre. The Sanger mapping group is providing clones to both sequencing pipelines as reported by Little (CIT:777934) and Grafham (CIT:777935). At the time of the meeting 10.1 Mb of unfinished and 3.7 Mb of finished sequence had been submitted to the public databases. Respective contributions by the GTC and Sanger groups were 6.5 and 3.6 Mb (unfinished) and 3.43 and 0.27 Mb (finished). Thiesen reported the generation of 300 kb of sequence in 10p11.2 and the subsequent analysis of the zinc finger gene cluster within it. The first mammalian sequence map of a centromere/chromosome arm boundary was reported by Guy et al (CIT:777929). The contiguous 1-Mb sequence template spans the junction between the centromere and the q arm and provides a logical termination point for the sequencing on 10q. Finally, Nikali reported their intention to sequence a region of circa 150-kb in 10q24 which is associated with IOSCA.

Diseases – Cancer

Since the last Workshop on human chromosome 10 mapping, 21 new diseases have been associated with this chromosome (Table 2). Furthermore, additional diseases (clinical phenotypes) have been associated with previously identified genes, i.e. PTEN and FGFR2. Recently, a locus associated with autosomal dominant lateral temporal epilepsy was assigned to 10q23→q24 (Pozza et al., 1999), in a region that overlaps with that corresponding to partial epilepsy (Ottman et al., 1995).

Multifactorial diseases – mapping

A number of multifactorial diseases have susceptibility loci which map to chromosome 10. These include a locus for inflammatory bowel disease on 10p (Hampe et al., 1999) and a new locus for IDDM (IDDM17) on 10q25 (Verge et al., 1998). In addition, there is suggestive evidence for two new loci involved in Alzheimer's disease, one by a linkage study on



chromosome 10q (Kehoe et al.,1999) and one by an association study on chromosome 10p12 (Zubenko et al., 1998). During the meeting, the mapping of four different multifactorial disorders which all mapped between markers D10S191–D10S604 on chromosome 10p12→q11.2, was discussed. Recently, linkage of obesity to chromosome 10p with a maximal multipoint LOD score of 4.85 was reported using extremely obese concordant sib pairs (Hager et al., 1998). Lee et al. (1999) have also obtained suggestive evidence for an additional obesity locus on chromosome 10q. Using a study group comprised of extremely obese children and adolescents of German origin, additional evidence that supports the existence of an important obesity locus on proximal chromosome 10p, was presented by Hinney et al. (CIT:777943). Evidence for linkage of chromosome 10p11.2 to type 1 diabetes has already been documented (IDDM10, Mein et al., 1998; Reed et al., 1997). Fine mapping and analysis of a candidate gene in this region was also discussed by Johnson (CIT:777947). Three independent groups have previously reported evidence of a schizophrenia locus mapping to chromosome 10p15→p11 (Straub et al., 1998; Schwab et al., 1998; Faraone et al., 1998). Transmission disequilibrium data with a marker, D10S211, that maps to the region of linkage, was presented by Wildenauer et al. (CIT:777942). Finally preliminary evidence suggesting that an important leprosy susceptibility locus maps to chromosome 10p12 was presented by Tosh et al. (CIT:777937).

Cancer/Tumor associated genes – deletion mapping studies

Since the last chromosome 10 workshop in 1997 four genes related to tumorigenesis have been newly identified, namely PTEN (also called MMAC1 or TEP1) in 10q23.3, LGI1 in 10q24, DMBT1 in 10q25 and ABI1 in 10p11.2.

The PTEN gene was independently cloned by three groups as a candidate tumor suppressor gene (Li and Sun,1997; Li et al., 1997; Steck et al., 1997). The protein product has homology with tensin/auxilin and a conserved structure of dual-specificity phosphatases. It has been shown to de-phosphorylate, among other candidate substrates, PIP3, and this activity has been associated with the tumor suppressor function of the gene. A high incidence of mutations or homozygous deletions have been reported in glioblastomas (14 to over 40%) and endome-

Fig. 1. Alignment of the genetic (Dib et al., 1996) and physical gene map (Deloukas et al., 1998). The framework markers (ordered with high confidence) of the gene map are indicated in bold face. The markers of the MD10 ABI Prism Linkage Mapping Set (medium density, 10 cM resolution) are underlined. The markers of the MD10 set together with those shown in italics compose the ABI Prism Linkage Mapping Set (medium density, 5 cM resolution). Progress in contig mapping is shown; the chromosome is divided in eight arbitrary intervals and for each of them, the number of bacterial clone contigs being sequenced at the Genome Therapeutics Corporation (GTC) and the Sanger Centre at the time of the meeting as well as their respective coverage in Mb is reported. The contig map shown here covers 64% of the total chromosome length (assuming an estimated size of 144 Mb).

trial carcinoma (30–50%), while the incidence appeared to be low in sporadic breast carcinomas, prostate cancers, thyroid carcinomas, SCLC, head and neck squamous cell carcinomas, melanomas, non-Hodgkin lymphomas, bladder cancers, hepatocellular carcinomas and colon cancers. Almost no mutations were found in NSCLC, pancreatic cancers, renal cancers, ovarian cancers and skin squamous cell carcinomas. Germline mutations/deletions have been reported in 30–80% of patients with Cowden disease and 50–60% of patients with Bannayan-Riley-Ruvalcaba syndrome, both of which are hereditary hamartomatous syndromes. There are several reports that different individuals from one family with a germline PTEN mutation may be affected by either of these two syndromes, suggesting that phenotypic manifestations of these diseases are one causal entity.

The LGI1 (Leucine-rich gene Glioma Inactivated) gene in 10q24 was cloned from the chromosome 10 breakpoint of a glioblastoma cell line carrying a translocation t(10;19)(q24; q13) leading to rearrangement of the LGI1 gene. Rearrangements of the LGI1 gene were detected in several glioblastomas. The gene is predominantly expressed in neural tissues. Its expression was shown to be reduced or absent in different brain tumors (Chernova et al., 1998).

The DMBT1 gene was described by Mollenhauer et al. (1997) and mutations were reported for gliomas. Screening in other cancers showed mutations only very sporadically. Recent reports claim that opsonin receptor for lung surfactant protein D (Holmskov et al., 1999), Hensin, CRP-ductin and DMBT1 (Takito et al., 1999) are different transcripts of the same gene. For lung, Wu et al. (1999) reported loss of expression of DMBT1 but only found one mutation (in cd 52) arguing that an unknown inactivating mechanism may be present. For esophageal and gastric cancers, Mori et al. (1999) found reduction or null expression in DMBT1 mRNA. However, homozygous deletion of the DMBT1 gene was only present in a small proportion of tumors.

The ABI1 gene, a human homologue to the mouse Abl-interactor 1, was found to be fused to the MLL gene in acute myeloid leukemia with t(10;11)(p11.2;q23) suggesting a role of this 10p11.2–specific gene in leukemogenesis (Taki et al., 1998).

The breakpoint map of recurrent chromosome aberrations in cancer according to the Mittelman-Catalogue is now available through the cCAP project at: http://www.ncbi.nlm.nih.gov/CCAP/mitelsum.cgi. Cancer-associated breakpoints have also been described on chromosome 10 in chromophobe renal cell carcinoma (Gunawan et al., 1999), and in follicular adenoma of the thyroid (not associated with the Ret proto-oncogene).

Since the last workshop, a series of deletion mapping studies have been performed to identify and narrow down critical regions harboring putative, unidentified tumor suppressor genes. In this workshop critical regions for deletion were discussed for glioma, lymphoma, and endometrial cancer (Siebert et. al., 1998; CIT:777945; Ichimura et al., CIT:777948; Monteiro et al., this workshop). An overview of the critical regions of deletion other than those affecting the above described tumor suppressor genes is given in Fig. 2.

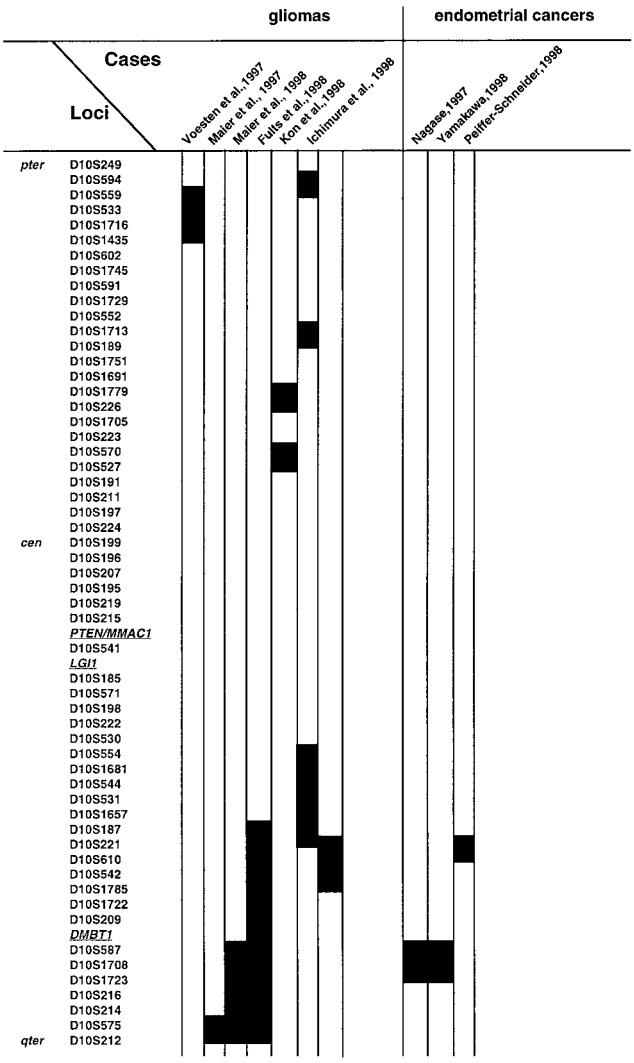


Fig. 2. Commonly deleted regions in gliomas and endometrial cancers (1997–1999).

Unbalanced chromosome 10 aberrations

Constitutional cytogenetic abnormalities of chromosome 10 resulting in pure chromosome 10 segmental imbalances are summarized in 10q22.2→q24.1 for trisomy. The affected individuals showed chromosomal dysmorphism syndromes, many of them presented with various malformations.

There are no breakpoints of terminal deletions proximal to q25, suggesting embryonic/fetal lethality of terminal deletions involving q24. The largest deletions (q11.2→q22.1) encompass about one third of the long arm. Most cases with terminal trisomies are due to malsegregation of a parental translocation and have a double segment aneuploidy. Pure trisomy 10p due to translocation to the short arm of an acrocentric chromosome has been described.

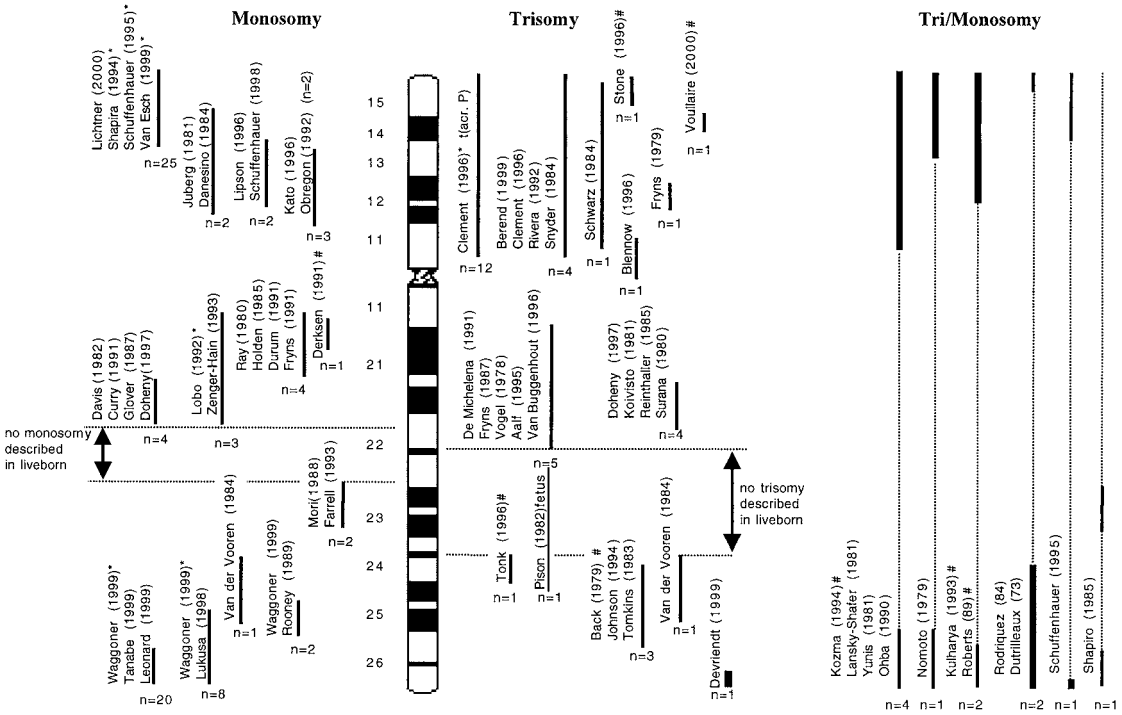


Fig. 3. Summary of published segmental anomalies of chromosome 10. The regions involved are roughly indicated by vertical bars and the number of index patients described is given. Unbalanced translocations involving the short arms of acrocentric chromosomes are considered as pure aneusomies of chromosome 10 segments. Chromosome 10 rearrangements with associated aneuploidies of other chromosomes are excluded. The breakpoints are given according to karyotype descriptions and/or figures in the respective references, the molecular data of some cases analysed are not presented. Review articles are marked with an asterisk. A single tetrasomy is listed (Devriendt et al., 1999). Double segment aneuploidies are given with a thick bar for the trisomic part and a thin bar for the monosomic part. Familial cases are indicated (#).

More than 30 (1993) cases of terminal trisomy 10q have been reported, which are double segment aneuploidies resulting from a parental translocation and are therefore not shown in Fig. 3 (Briscioli et al., 1993; Chen et al., 1999; Fryns et al., 1987). There are at least seven cases with ring chromosome 10 (r(10)(p15q26)) in the literature (reviewed by Calabrese et al., 1994 and Shapira et al., 1994). Mosaic trisomy 10 has been described in six liveborn, all reported cases of non-mosaic trisomy 10 have been associated with fetal death (Boon et al., 1996). A unique abnormality of chromosome 10 suggesting the presence of a latent intercalary centromere within 10q25 was described in a mentally retarded boy (Voullaire et al., 1993).

Bioinformatics – WWW resources

The Internet, and in particular the World Wide Web (WWW), supports a wealth of resources for genome investigators and has become a primary channel for the exchange of information. Talbot (CIT:777931) reported on the continuation of the Genome Database (GDB) project. The database has moved to the Hospital for Sick Children, Toronto, Canada and is available at www.gdb.org/. GDB in collaboration with HUGO has created chromosome specific WWW pages which list links to sites that make available relevant data on areas such as mapping, sequencing, and sequence annotation. The chromosome 10 page is available at http://www.gdb.org/hugo/chr10/. Scott (CIT:777933) presented 10ace which is an ACEDB-based database and contains the mapping and sequence data generated by the chromosome 10 project at the Sanger Centre (ftp://ftp.sanger.ac.uk/pub/human/chr10/RELEASES/). The database can also be accessed on the WWW via the Webace or Acebrowser (http://webace.sanger.ac.uk/cgi-bin/ace/simple/10ace). Hubbard (CIT:777936) reported on a real-time automatic sequence analysis system, which is being applied to all of the working-draft sequence and aims to provide a consistent view of the human genome. The project which is a collaboration between the Sanger Centre and the EBI and is called EnsEMBL, went live on January, 27 and is available at http://www.ensembl.org/. Koufaki (CIT:777941) reported the construction of a database tool for handling mutation analysis data and its application for PTEN, PTENP1 (mapped to 9p21) and LGI1.

Acknowledgements

We thank all workshop participants for their help and would particularly like to acknowledge the contributions of K. Ichimura, R. Siebert, and C. Talbot.

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Abstract titles of the third international workshop on human chromosome mapping and sequencing 1999

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High resolution physical mapping and sequence-ready BAC contigs in the gene-rich region 10q23.3→q25.1 (CIT:777927)

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Genomic sequencing of KOX zinc finger gene cluster on chromosome 10p11.2 (CIT:777928)

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1 Mb of genomic sequence spanning the centromere/ chromosome arm boundary in 10q11 (CIT:777929)

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A refined physical map of the NFKB2/HOX11/PAX2 region in chromosome band 10q24 (CIT:777930)

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Continuation of the genome database project (CIT:777931)

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The human chromosome 10 project (CIT:777932)

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The chromosome 10 database, (10ace) (CIT:777933)

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Chromosome 10 sequencing at Genome Therapeutics Corporation (CIT:777934)

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Sequencing and finishing of chromosome 10 at the Sanger Centre (CIT:777935)

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Automating the analysing of the human genome sequence (CIT:777936)

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A genome scan for Major Leprosy susceptibility genes (CIT:777937)

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A new gene involved in DNA double-strand break repair and V(D)J recombination is located on human chromosome 10p (CIT:777938)

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From the Digeorge-like syndrome to the HDR-syndrome (CIT:777939)

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Establishment of a PAC contig across the DGS2 region on 10p and mapping of an HDR syndrome locus distal to DGS2 (CIT:777940)

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Mutation database of three genes located on chromosome 10q23→q24 (CIT:777941)

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Potential susceptibility gene locus for schizophrenia on 10p: searching for candidate genes (CIT:777942)

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Suggestive evidence for a major locus for obesity on chromosome 10 (CIT:777943)

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Physical mapping and determination of a chromosomal breakpoint at 10q26.3→qter caused by an acrocentric translocation in a patient with psychomotor retardation and dismorphic features (CIT:777944)

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Characterization of structural alterations in lymphatic neoplasms and mapping of a constitutional breakpoint in 10q23→q25 by means of fluorescence in situ hybridization (CIT:777945)

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Fine physical and transcriptional mapping and positional candidate gene analyses of the gene loci for IOSCA and adPEO diseases (CIT:777946)

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Mapping a type 1 diabetes susceptibility locus – IDDM10 (CIT:777947)

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A detailed deletion mapping and a PTEN gene mutation analysis suggest the existence of a second tumour suppressor gene for human astrocytic glioma on chromosome 10 (CIT:777948)

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Evaluation of markers on human chromosome 10, including the homologue of the rodent RF-I gene, for linkage to ESRD in African American patients (CIT:777949)

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