Eur J Hum Genet 1994;2:193–252

N.K. Spurr[a]
S.P. Bryant[a,g]
J. Attwood[b,g]
K. Nyberg[a,g]
S.A. Cox[a]
A. Mills[a]
R. Bains[a]
D. Warne[a]
L. Cullin[a]
S. Povey[b]
J.-M. Sebaoun[c,e]
J. Weissenbach[d]
H.M. Cann[e]
M. Lathrop[c,e,f]
J. Dausset[e]
A. Marcadet-Troton[e]
D. Cohen[e]

European Gene Mapping Project (EUROGEM): Genetic Maps based on the CEPH reference families

[a] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), Clare Hall Laboratories, South Mimms, UK;
[b] MRC Human Biochemical Genetics Unit, University College London, UK;
[c] INSERM U.358, Paris, France;
[d] Généthon, Evry, France;
[e] Fondation Jean Dausset - CEPH, Paris, France;
[f] Present Address: Wellcome Trust Centre for Human Genetics, Oxford, UK;
[g] These authors contributed equally to the work.

The European Gene Mapping (EUROGEM) Project was conceived in 1988 by the EC Working Party on Human Genome Analysis with the objective to produce a 5cM human gene map. The Working Party agreed that there existed in Europe the necessary resources to make a major contribution to the human gene map which could complement existing initiatives and provide important technology transfer between member states. While many laboratories were mapping individual disease loci, there was a need for co-ordination of this work and for the distribution of DNA probes and other materials between laboratories. It was proposed that two EUROGEM resource centres and a network of laboratories be established to carry out this work. The proposal was accepted by the European Commission and contracts issued in 1991 (Contracts: GENO-0001 and GENO-0002 (Resource centres), GENO-CT91-0007 (Network laboratories)).

The project has been structured around two resource centres and a network of laboratories carrying out genotyping. The two resource centres were;

1) Human Genetics Resources Laboratory (HGR), Imperial Cancer Research Fund (ICRF), Clare Hall, South Mimms, Hertfordshire, UK

2) Centre d'Étude du Polymorphisme Humain (CEPH), Paris, France

A total of 22 laboratories were sub-contracted to carry out genotypic analysis. All the Network laboratories were sub-contracted to type a total of 81 markers in 24 months, on the complete panel of 40 CEPH reference families [1]. To encourage groups to type the most informative markers, a weighting scheme was devised as follows:

1) Markers with a heterozygote frequency of less than 70% were equivalent to one marker;

2) Markers with a heterozygote frequency between 70-80% were equivalent to two markers;

3) Markers with a heterozygote frequency above 80% were equivalent to three markers.

Biological resources

The distribution of materials used within the project was organised through the two resource cen-

Received:
July 22, 1994
Accepted:
August 3, 1994

Dr. Nigel Spurr
Human Genetic Resources Unit
Imperial Cancer Research Fund
Blanche Lane, South Mimms, Potters Bar
Herts, EN6 3LD (UK)

1018–4813/94/
0023–0193$8.00/0

tres: the Probe Resource Centre, located in the HGR laboratory at ICRF and the DNA Resource Centre, located at CEPH in Paris. The Probe Resource Centre was also responsible for the overall co-ordination of the project and for the transfer of genotype data to CEPH for inclusion in the CEPH database.

The DNA Resource Centre provided the network laboratories with DNA from the original 40 CEPH reference families. The DNA was distributed either in microtitre plates for PCR analysis, or as restriction digests transferred onto membranes ready for Southern blotting. In total, 22 different restriction enzymes were used; all laboratories received membranes with MspI and TaqI digests, and a further 3-4 membranes with digests of their choice determined by which probes they were planning to use.

The markers used for linkage analysis came from two sources: the network laboratories had a commitment to supply some markers for their own use, and the Probe Resource Centre supplied the rest. The first distribution by the Probe Resource Centre took place in September 1991 and consisted of 74 DNA probes for Southern blotting and 35 PCR formatted markers. Some of the latter detected simple two-allele RFLPs, although microsatellites were becoming increasingly more common. The markers were selected from the collection held at the Probe Resource Centre. The main criterion for selection was that the markers should not have been screened previously across the CEPH panel. Particular importance was also given to including markers within or close to coding regions for known genes, so that these could be located on the genetic map. The spacing of markers was also considered; whenever possible we tried to fill in gaps in the existing maps. We requested all markers designated as reference markers in HGM11 from the originators, and those made available to us were included in the project.

The second consignment of markers, distributed to the network laboratories in early 1992, reflected the way in which genetic linkage analysis was developing: the PCR based markers detecting highly informative microsatellites outnumbered the DNA probes. Subsequent markers distributed by the Probe Resource Centre were with a few exceptions PCR formatted. The exceptions include markers designated as reference markers in HGM11, and highly informative minisatellites.

The PCR formatted markers were selected by screening literature and databases. As previously, markers which had not been screened across the CEPH panel were chosen. With the increasing number of microsatellites published, it was also possible to select for high informative value in addition to the criteria already mentioned; most PCR formatted markers thus selected had an observed heterozygote frequency of 70% or above.

With the publication of the Généthon microsatellite map [2], a valuable new source of markers for the EUROGEM project became available. These markers had only been screened across a core of 8 families, and this could be extended by the Network laboratories to include the remaining 32 families. This would also integrate the new markers into a more general map. An agreement was reached with Généthon to use the markers in this project, and the first 206 markers obtained are included in the present map. These markers were selected for high heterozygosity, and also for spacing along the chromosome to give markers at approximately 10 cM intervals.

Genotyping and Data Collection

One of the requirements for those participating in this project was that all the genotype data produced during this project were to be made freely available. This was achieved by depositing all the data with CEPH for inclusion in their public database. To assist with this work a significant amount of time has been devoted to ensuring all laboratories had sufficient hardware and software. The laboratories were encouraged to establish a connection to the Internet network, and this was used to exchange information between laboratories and the co-ordinating centres. Only two laboratories at present are not connected to Internet and we aim to have a 100% connectivity during the second phase of the project which started in May 1994.

Each of the 22 network laboratories was supplied with a Unix workstation (DECStation 5000/25, Digital Corporation). This included a run-time version of the Sybase relational database management system (Sybase Inc), together with a Sybase application called GENBASE (Mark Lathrop and Jean-Marc Sebaoun, unpublished), and the version 6 CEPH database in Sybase format.

Each laboratory typed a number of markers across the CEPH panel, following the usual CEPH rules about typing informative families [1]. The data were

collated mostly by the GENBASE software but some laboratories used the MS-DOS CEPH database programs, and uploaded electronically to a central ftp server (diamond.gene.ucl.ac.uk), accessible to all the network laboratories.

From here, the files were transmitted electronically to CEPH for inclusion in the main CEPH database. Those labs not networked at the time submitted their data on floppy disks.

The submitted data, in either Unix or PC dump format, were concatenated to a single file and then broken down into separate files by chromosome. Unix scripts (JA, unpublished) were used to process these files into a format very similar to that used by the LINKAGE suite of programs, which were then analysed by the LINK2SUM program (JA, unpublished) which performs the same checks and calculations as the original CEPH SUMDAT.EXE program. Allelic exclusions detected were reported back to the collaborating laboratories, the necessary corrections edited into the submitted data files and the LINKAGE format files regenerated. CRI-MAP input files were produced from these corrected files using the program LINK2CRI (JA, unpublished) and placed on the ftp server for downloading by the laboratories making the maps.

In all, data on 576 markers were submitted (table 1). These corrected data are available in CRI-MAP format by anonymous ftp from mahler.clh.icnet.uk in /pub/eurogem/mapdata and from CEPH.

Map Construction

Following the data collection phase, a process of map construction was initiated. Each network laboratory was assigned one or more of the 22 autosomal chromosomes or chromosome X. The aim was to place the new EUROGEM markers on a well-supported framework map which could be composed of selected CEPH markers, Généthon CA repeats or Cooperative Human Linkage Center (CHLC) systems [3,4].

Laboratories made their own choice as to which framework to choose (CEPH or CHLC) and their reasons are detailed in the sections for each chromosome. The main task was to place as many as possible of the newly typed EUROGEM markers on the base map with 1000:1 support.

Each laboratory adopted a particular strategy for producing the map, described in the section for each chromosome. CRI-MAP version 2.4 [5] was used by all but two of the laboratories. Map-building began in parallel with the elimination of allelic exclusions, with corrections being reported so that the data could be corrected and the CRI-MAP input files regenerated on a continuous basis. Most labs used the CRI-MAP 'build' routine to enlarge their maps. In the course of mapbuilding, intralocus recombinants were detected and reported back to the contributing laboratories who, in turn, fed corrections back to the central site. Considerable advantage was derived from most sites being connected to the Internet, as communication by electronic mail between labs was mostly very fast, and corrected datafiles could be downloaded within a few hours of requesting corrections. Additionally, help and advice from those more experienced in mapbuilding could be obtained quickly and easily, and problems with using the software diagnosed and solved. As the maps stabilised, unusual clusters of recombinants could be detected using the 'chrompic' option of CRI-MAP, and further rounds of error-checking and correction were carried out. In cases where it was impossible to verify the data and strong doubts still remained as to their validity, they were removed from the data-files.

As well as regular checking throughout for local support of at least 1000:1 with CRI-MAP's 'flips2' option, the final maps were checked with 'flips4' to ensure that alternative orders had been sufficiently explored. For those markers which could not be placed with 1000:1 support, CRI-MAP 'all' runs were conducted for each to determine the range of positions that fell within the 3-unit support interval.

When complete, the CRI-MAP output files were uploaded by ftp and transformed into PostScript figures by a set of Unix scripts (JA and SPB, unpublished). The framework maps were juxtaposed with 800-band ideograms (G. Spowart, unpublished) and a representative set of cytogenetic data chosen from GDB to map the relationship between the ideograms and the maps.

The support intervals for those markers which could not be placed uniquely were plotted separately. These figures accompany each of the individual chromosome reports.

Training workshops

As indicated above, one of the aims of this project has been to disseminate technical knowledge through

the European community. This has led us to organise two training workshops.

At the first EUROGEM meeting, which was held in London on 19 August 1991 in connection with HGM11, interest was expressed in training, with particular emphasis on computing and PCR techniques. At the time, PCR was still not much in use and some laboratories had no first-hand experience of the technique. The first workshop was organised by the Probe Resource Centre in collaboration with CEPH and Généthon, and took place at Généthon in December 1991. Its purpose was to teach technicians and young scientists involved in the project the use of PCR in linkage analysis. The computing workshop took place near Heidelberg in June 1993 and was organised in collaboration with the European Data Resource for Human Genome Research, DKFZ, Heidelberg. The workshop programme included UNIX system management, data management with GENBASE and linkage analysis with LINKAGE and CRI-MAP.

Meetings

To assist with the coordination of the project and to keep the whole group up to date on progress, an annual meeting has been held. These have been organised locally by one of the network laboratories with help from the project coordinator (NKS).

A preliminary meeting was held in London on 19 August 1991 in connection with HGM11. At this meeting, the working methods of the collaborative project were established and a timetable set out. The first EUROGEM meeting was held in Barcelona, over the period 1-3 October 1992. This meeting included both scientific and general matters and included invited speakers from outside the collaboration. The second EUROGEM meeting took place in Cork, during 1-3 October 1993. The programme followed the same pattern as the first meeting and included oral and poster presentations as well as general discussions about the project.

Acknowledgements

The EUROGEM project would like to thank the European Commission for sponsoring this project under DGXII, Human Genome Analysis programme. In particular we acknowledge the assistance of Mr. Andreas Klepsch and Drs. Bronwen Loder and Manuel Hallen in helping us understand the application forms and for their help with the organisation of meetings for the whole group during the past three years. We would also like to acknowledge the generous support of the Digital Corporation with the computers and in funding the training workshop in Heidelberg. The Probe Resource Group at ICRF would like to thank those who have assisted in the laboratory including, Tariq Raman, Paul Bodfish and Irina Dianova.

JA and SP would like to thank the MRC Human Genome Mapping Project for additional computing support.

Chromosome 3 : We would like to thank Drs. N. Porchet and J. P. Aubert for MUC4 probe. We would also like to thank the Deutsche Forschungsgemeinschaft (GA 210/6-1) and the Medizinische Universität zu Lübeck for financial support.

Chromosome 5 : This work was also supported by the Fondo de Investigaciónes Sanitarias (FIS) and the Comisión Interministerial de Ciencia y Tecnológia (CICYT) from Spain and the Association Française contre les Myopathies from France.

Chromosome 6 : We are grateful to JA for his invaluable help in running CRI-MAP. The technical assistance of C. Grottoli was greatly appreciated.

Chromosome 7 : We would like to thank J. R Gum for the MUC3 probe and Dr. A. Henney for ELN genotyping data.

Chromosome 8 : The CEPH Consortium Chromosome 8 committee for access to the error checked CEPH consortium chromosome 8 database

Chromosome 9 : We would like to thank the following individuals for genotyping data: Owen Rose, Duncan Franklin, Stavros Malas, A. Ashworth, Joanne Lyerla, R. Gunaseelan and Una Fairbrother.

Chromosome 10 : Funded through the EUROGEM project and the Hellenic Secretariat for Research and Technology. We thank: JA and SB for their advice with the map building; AM-T, KN and JMS for making available CEPH DNA samples, primers and the GENBASE programme, respectively; G.Houlaki for secretarial assistance.

Chromosome 11 : We would like to thank Drs. N. Porchet and J. P. Aubert for MUC5 probe. We would also like to thank Drs. M. Litt and P. Kramer for allowing us to use their corrected CEPH database.

Chromosome 12 : We thank B. Riley and R. Williamson for the contribution of data for markers D12S58 and D12S63, the EUROGEM project (PL93-0107) and the Fondo de Investigaciónes de la Seguridad Social (92/0885E). VA was supported by fund-

ing to Jacques Beckmann. JA is acknowledged for help in map construction.

Chromosome 13 : This work was supported by the EC EUROGEM project and the Netherlands Organisation for Scientific Research (NWO). We thank Dr. A. Reis for sharing primer sequences before publication and Taco P. Jesse for help with genotyping. Drs. A.M. Bowcock and S.E. Antonarakis are acknowledged for submitting their genotype data to CEPH.

Chromosome 14 : We would like to thank Dr. Diane Cox for allowing us to use her corrected CEPH database.

Chromosome 15 : We would like to thank Dr. Chee Gee See for the FISH assignment of D15S105 (See, unpublished).

Chromosome 21 : We would like to thank B. Riley and R. Williamson for the contribution of data for marker D21S156, the EUROGEM project (PL93-0107), EV grant GENO CT-930015 and the Fondo de Investigaciónes de la Seguridad Social (92/0885E). APS was supported by funding to Jacques Beckmann. JA is acknowledged for help in map construction.

Figures

Figures 1-23 show ideograms of each human chromosome along with the framework maps showing the order of markers supported at 1000:1. These orders and the recombination fractions between them are shown as male, female and sex averaged. The distances between markers is shown to scale. Loci haplotyped together are shown on the same line. Cytogenetic localisation of markers is shown for most chromosomes. This information was obtained from GDB and the localisations were derived using alternative techniques, mainly fluorescent in-situ hybridisation or somatic cell hybrid mapping. This information was not available for all chromosomes as the markers used had only been mapped by linkage. The markers typed during the EUROGEM project are indicated in bold type. Inset into each figure is a simplified representation of the framework map with markers equally spaced. To the right of these maps is indicated the positions of markers which could not be uniquely placed in the framework maps. The thickness of the bars indicates the statistical support for each interval. The most likely interval, and others with a log-likelihood difference of less than 1 from it, is shown with a broad line. Intervals with a log-likelihood difference between 1 and 2 compared to the best have a narrower line. Intervals with a log-likelihood difference of between 2 and 3 compared to the best are indicated by a fine line. Dashed lines connect non-adjacent intervals.

The inset maps of chromosomes 12 and 21 contain some non-EUROGEM typed markers. These are index markers and were used to help with the integration of the maps.

Tables

Table 1 shows a listing of all the markers typed during the EUROGEM project. There are some markers in this list which do not appear in the final maps. This was due to incomplete typings, or data inconsistencies that could not be resolved.

Consortium Laboratories

The addresses of all EUROGEM collaborating laboratories are given below. The abbreviated name of the laboratory, which is also used in the Lab column of table 1, is a unique code which was used to name the Sybase database server and to tag the contributions made by each laboratory. The laboratory of Dr. Mike Dixon is participating in the second phase of EUROGEM but kindly submitted typing data early enough to be incorporated in the phase I maps, and so is included here.

leiden — Dr. E. Bakker
Leiden University
Department of Human Genetics
Sylvius Laboratory
P.O. Box 9503
2300 RA Leiden
The Netherland

milou — Drs. Howard M. Cann, Daniel Cohen and Mark Lathrop
C.E.P.H.
27, rue Juliette Dodu
75010 Paris
France

cagliari — Professor Licinio Contu
Università degli Studi di Cagliari
Istituto di Clinica Medica
Via San Giorgio, 12
09124 Cagliari
Italy

barcelona
Dr. X. Estivill
Molecular Genetics Department (IRO)
Hospital Duran i Reynals
Crta. Castelldefels Km 2,7
08907 Hospitalet
Barcelona
Spain.

cambridge
Professor M.A. Ferguson-Smith
Cambridge University
Department of Pathology
Tennis Court Road
Cambridge
CB2 1QP
UK

lubeck
Dr. Andreas Gal
Institut für Humangenetik
Medizinische Universität zu Lübeck
Ratzeburger Allee 160
2400 Lübeck 1
Germany

marburg
Prof. Dr. K.-H. Grzeschik
Klinikum der Philipps
Universität Marburg
Institut für Humangenetik und Humangenetische
Poliklinik
Bahnhofstrasse 7A
3550 Marburg
Germany

caerdydd
Dr. Helen Harley
University of Wales College of Medicine
Institute of Medical Genetics
Heath Park
Cardiff
CF4 4XN
UK

dublin
Dr. Peter Humphries
University of Dublin
Department of Genetics
Lincoln Place Gate
Trinity College
Dublin 2
Ireland

aarhus
Dr. T. Kruse
University of Aarhus
Institute of Human Genetics
The Bartholin Building
8000 Aarhus C
Denmark

lisboa
Dr. J. Lavinha
Human Genetics Laboratory
Instituto Nacional de Saúde Dr. Ricardo Jorge
Av. Padre Cruz
1699 Lisboa Codex
Portugal

cork
Dr. T. McCarthy
Department of Biochemistry
University College
Lee Maltings
Prospect Row
Cork
Ireland

madrid
Dr. F. Moreno
Departamento de Genética Molecular
Hospital Ramón y Cajal
28034 Madrid
Spain

crete
Dr. Nicholas Moschonas
Foundation for Research & Technology
Institute of Molecular Biology and Biotechnology
P.O. Box 1527
711 10 Heraklion
Crete

mrchbgu
Dr. Sue Povey
MRC Human Biochemical Genetics Unit
University College London
Wolfson House
4 Stephenson Way
London
NW1 2HE
UK

groningen
Dr. H. Scheffer
University of Groningen
Department of Medical Genetics
Antonius Deusinglaan 4
9713 AW Groningen
The Netherlands

icrf
Dr Nigel Spurr
Human Genetic Resources
ICRF Clare Hall Laboratories
Blanche Lane
South Mimms
Herts EN6 3LD
UK

roma
Prof. Luciano Terrenato
Dipartimento di Biologia
Università "Tor Vergata" di Roma
Via Emanuele Carnevale
00173 Roma
Italy

bouchet
Dr. Gilles Vergnaud
Lab. de Génétique des Espèces
Plateau Technique CHR
Quai Moncousu
44035 Nantes Cédex
France

pasteur
Dr. J. Weissenbach
Généthon
1 Rue de L'Internationale
BP 60
F-91002 EVRY
Cédex 2
France

marys
Professor R. Williamson
Dept. of Biochemistry & Molecular Genetics
St. Mary's Hospital Medical School
Norfolk Place
London
W2 1PG
UK

edinburgh
Dr. Alan Wright
Human Genetics Unit
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU
UK

dixon
Dr Mike Dixon
Dept. of Cell and Structural Biology
3rd Floor, Stopford Building
University of Manchester
Oxford Road
Manchester M13 9PL UK

Table 1. Markers typed for EUROGEM

Lab	Probe	Enzyme	Symbol	Ch.
aarhus	9112	BclI	S100A7	1
aarhus	Psor	MspI	S100A7	1
cork	AFM205ta11	(CA)n	D1S236	1
cork	AFM234wf6	(CA)n	D1S249	1
dublin	D1S103	PCR	D1S103	1
dublin	D1S104	PCR	D1S104	1
dublin	AT3	PCR	AT3	1
bouchet	CEB10	HinfI	D1S153	1
bouchet	CEB15	PvuII	D1S172	1
bouchet	CEB20	PvuIH/HinfI	D1S173	1
bouchet	CEB37	HaeIII	D1S33	1
bouchet	CEB55	HinfI	D1F101S2	1
bouchet	CEB82	HinfI	D1S338	1
bouchet	CEB88	HaeIII	D1S339	1
bouchet	CEB9	HaeIII	D1F35S2	1
bouchet	CEB98	PvuII	CEB98	1
mrchbgu	PGD-H1	BamHI	PGD	1
aarhus	AFM119xc7	(CA)n	D2S126	2
aarhus	AFM177xh4	(CA)n	D2S139	2
aarhus	AFM218zg3	(CA)n	D2S159	2
aarhus	pKM1400	PstI	COL4A3	2
aarhus	pMM19-1-4	BamHI	COL4A4	2
aarhus	pMM19-1-4	TaqI	COL4A4	2
bouchet	CEB75	HaeIII	CEB75	2
cagliari	AFM052xf8	(CA)n	D2S114	2
cagliari	AFM087xa1	(CA)n	D2S121	2
cagliari	AFM112yd4	(CA)n	D2S125	2
cambridge	AFM220ze3	(CA)n	D2S160	2
cambridge	AFM225zg5	(CA)n	D2S162	2
aarhus	ALP-1	RsaI	ALPP	2
aarhus	GCG	(GA)n	GCG	2
bouchet	CEB1	HinfI	D2S90	2
bouchet	CEB54	HinfI	D2S229	2
bouchet	MCT106	PvuII	D2S61	2
leiden	PROC	RsaI	PROC	2
mrchbgu	LCT	SSCP	LCT	2
mrchbgu	pynh24	Msp1	D2S44	2
cambridge	D3S1038	(CA)	D3S1038	3
cambridge	AFM220yh4	(CA)n	D3S1300	3
cambridge	AFM225yd6	(CA)n	D3S1303	3
dublin	10CA	(CA)n	D3S1447	3
dublin	PAPA	PCR	ACPP	3
dublin	RHO	PCR	RHO	3
dublin	13CA	(CA)n	D3S1449	3
dublin	23CA	(CA)n	D3S1448	3
dublin	4CA	(CA)n	D3S1450	3
bouchet	CEB32	HaeIII	D3S1475	3
bouchet	CEB44	HinfI	D3S1476	3
dublin	RAJ1	PCR	D3S621	3
leiden	HRG	(CA)n	HRG	3
mrchbgu	JER64	PvuII	MUC4	3
mrchbgu	SIC	PstI	SI	3
lubeck	AFM057xc5	PCR	D3S1261	3
lubeck	AFM059xa9	PCR	D3S1262	3
lubeck	AFM079yg5	PCR	D3S1263	3
lubeck	AFM087yb7	PCR	D3S1265	3
lubeck	AFM126zc5	PCR	D3S1271	3
lubeck	AFM164we1	PCR	D3S1277	3
lubeck	AFM164yg9	PCR	D3S1279	3
lubeck	AFM179xh10	PCR	D3S1282	3
lubeck	AFM217xd2	PCR	D3S1297	3
lubeck	ACPP	PCR	ACPP	3
lubeck	CRBPI	TaqI	RBP1	3
lubeck	D3S1246	PCR	D3S1246	3
lubeck	Mfd4	PCR	SST	3
leiden	AFM135xc3	(CA)n	D4S398	4

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
leiden	AFM157xg3	(CA)n	D4S403	4
leiden	AFM161yf6	(CA)n	D4S405	4
leiden	AFM164tf6	(CA)n	D4S406	4
leiden	AFF165xc11	(CA)n	D4S408	4
leiden	LR12	PstI	LR12	4
leiden	MH34	(CA)n	D4S243	4
leiden	VC63	TaqI	D4S129	4
leiden	E9p1	MspI	D4S112	4
mrchbgu	DRD5CAn	(CA)n	DRD5	4
bouchet	CEB38-61	HaeIII	D4S1100	4
leiden	BJ56	(CA)n	D4S127	4
leiden	C39	(CA)n	D4S43	4
leiden	GABRB1	(CA)n	GABRB1	4
leiden	pYNZ32	VNTR	D4S125	4
marys	GABRA2	(CA)n	GABRA2	4
bouchet	CEB8	HaeIII	D4F35S1	4
leiden	FABP2	(CA)n	FABP2	4
leiden	M6.1	MspI	D4S14	4
leiden	MFD140	(CA)n	D4S192	4
leiden	MFD22	(CA)n	D4S171	4
leiden	MFD59	(CA)n	D4S174	4
bouchet	AFM028xb12	(CA)n	D5S392	5
bouchet	AFM042xd12	(CA)n	D5S393	5
bouchet	AFM112yb6	(CA)n	D5S400	5
bouchet	AFM163xa11	(CA)n	D5S407	5
bouchet	AFM164xb8	(CA)n	D5S408	5
bouchet	AFM184yb6	(CA)n	D5S409	5
bouchet	AFM191xd8	(CA)n	D5S410	5
bouchet	AFM205wh10	(CA)n	D5S416	5
bouchet	CSF1R	(CA)n	CSF1R	5
bouchet	D5S356	(CA)n	D5S356	5
bouchet	FGFA	(CA)n	FGF1	5
madrid	268	(CA)n	D5S268	5
madrid	AFM028xb12	(CA)n	D5S392	5
madrid	AFM042xd12	(CA)n	D5S393	5
madrid	AFM066xf11	(CA)n	D5S396	5
madrid	AFM095zb7	(CA)n	D5S398	5
madrid	AFM112yb6	(CA)n	D5S400	5
madrid	AFM116xe1	(CA)n	D5S401	5
madrid	AFM127xh4	(CA)n	D5S402	5
madrid	AFM154xg3	(CA)n	D5S406	5
madrid	AFM163xa11	(CA)n	D5S407	5
madrid	AFM164xb8	(CA)n	D5S408	5
madrid	AFM177xb4	(CA)n	D5S477	5
madrid	AFM184yb6	(CA)n	D5S409	5
madrid	AFM191xd8	(CA)n	D5S410	5
madrid	AFM193xe11	(CA)n	D5S411	5
madrid	AFM198we11	(CA)n	D5S412	5
madrid	AFM203xa7	(CA)n	D5S415	5
madrid	AFM205wh10	(CA)n	D5S416	5
madrid	AFM205wh8	(CA)n	D5S417	5
madrid	AFM205zh4	(CA)n	D5S418	5
madrid	AFM207yc1	(CA)n	D5S419	5
madrid	AFM210vd6	(CA)n	D5S421	5
madrid	AFM211yc7	(CA)n	D5S422	5
madrid	AFM212yb8	(CA)n	D5S489	5
madrid	AFM214xe9	(CA)n	D5S626	5
madrid	AFM214yg1	(CA)n	D5S490	5
madrid	AFM214zg9	(CA)n	D5S424	5
madrid	AFM220yg5	(CA)n	D5S494	5
madrid	AFM224zh2	(CA)n	D5S822	5
madrid	AFM238we11	(CA)n	D5S426	5
madrid	AFM238xe11	(CA)n	D5S498	5
madrid	AFM238xf4	(CA)n	D5S428	5
madrid	AFM242xb10	(CA)n	D5S429	5
madrid	AFM254yb5	(CA)n	D5S431	5

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
madrid	AFM255xb9	(CA)n	D5S432	5
madrid	AFM276wd5	(CA)n	D5S434	5
madrid	AFM281yh9	(CA)n	D5S637	5
madrid	AFM283wb5	(CA)n	D5S640	5
madrid	AFM302yg5	(CA)n	D5S652	5
madrid	B153	MspI	B153	5
madrid	CA236	(CA)n	D5S1356	5
madrid	CRI-L407	TaqI	D5S63	5
madrid	CRI-LM4	BamHI	CRI-LM4	5
madrid	CSF1R	(CA)n	CSF1R	5
madrid	D5S107	(CA)n	D5S107	5
madrid	D5S203	(CA)n	D5S203	5
madrid	D5S204	(CA)n	D5S204	5
madrid	D5S208	(CA)n	D5S208	5
madrid	D5S260	(CA)n	D5S260	5
madrid	D5S346	(CA)n	D5S346	5
madrid	D5S353	(CA)n	D5S353	5
madrid	HMGCoAR	(CA)n	HMGCR	5
madrid	IL-9	(CA)n	IL9	5
madrid	AFM273yf1	(CA)n	D5S433	5
marys	gabra6	(CA)n	GABRA1	5
mrchbgu	CK9	HinfI	CK9	5
bouchet	16C2	HinfI	D5S206	5
bouchet	CEB28	HinfI/HaeIII	D5S347	5
roma	AFM238we11	(CA)n	D5S426	5
bouchet	CEB77	HaeIII	D5S555	5
leiden	CA26	(CA)n	D5S299	5
leiden	cCB83	(CA)n	D5S112	5
leiden	cJW25.1	(CA)n	D5S318	5
leiden	cYN5.64	(CA)n	D5S82	5
manchester	2C7	(CA)n	D5S365	5
manchester	2D10	(CA)n	D5S376	5
manchester	2G10	(CA)n	D5S378	5
manchester	90HA	(CA)n	D5S519	5
manchester	E5.12	(TAA)n	D5S373	5
manchester	FGFA	(CA)n	FGF1	5
manchester	IG106	(CA)n	IG106	5
manchester	IG137	(CA)n	IG137	5
manchester	IG22	(CA)n	IG22	5
manchester	IG34	(CA)n	IG34	5
manchester	IG611	(CA)n	IG611	5
manchester	IG82	(CA)n	IG82	5
manchester	IG9	(CA)n	IG9	5
manchester	IG_52	(CA)n	D5S527	5
manchester	MFD116	(CA)n	D5S209	5
manchester	MFD154	(CA)n	D5S211	5
manchester	RPS14	(CA)n	RPS14	5
manchester	SPARC	(CA)n	SPARC	5
manchester	csf.tet	(CA)n	CSF1R	5
manchester	n5.61	(CA)n	D5S372	5
manchester	n5.64	(CA)n	D5S379	5
marys	gabra1	(CA)n	GABRA1	5
milou	AFM-cack	ca	CKMT2	5
roma	AFM210vd6	(CA)n	D5S421	5
roma	AFM214zg9	(CA)n	D5S424	5
cagliari	PIM_5R1	TaqI	PIM	6
cagliari	pJCZ30	TaqI	D6S37	6
roma	AFM035wc1	(CA)n	D6S259	6
roma	AFM144yf2	(CA)n	D6S274	6
roma	AFM299ye5	(CA)n	D6S288	6
roma	AFM56xe1	(CA)n	D6S260	6
roma	CO91100	(CA)n	D6S202	6
roma	rep	(CA)n	SCA1	6
dublin	RDS	PCR	RDS	6
cagliari	AFM136yf8	(CA)n	D6S271	6
cagliari	AFM158ye9	(CA)n	D6S276	6

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
cagliari	AFM158yh2	(CA)n	D6S277	6
cagliari	pAT-A	HindIII	C4A	6
milou	AFM200wc9	(CA)n	D6S289	6
milou	CPHD1	(CA)n	EDN1	6
milou	GZ-3/GZ-4	(CA)n	TUBB	6
milou	cCI6-15	RsaI	D6S143	6
milou	cCI6-5	TaqI	D6S137	6
milou	cCI6-50	BglII	D6S162	6
milou	cCI6-64	TaqI	D6S171	6
milou	cCI6-77	PstI	D6S177	6
milou	cCI6-95	RsaI	D6S188	6
bouchet	CEB26	PvuII	D6S227	6
bouchet	CEB3	HinfI/HaeIII	D6S132	6
bouchet	CEB4	HinfI/PvuII	D6S133	6
cagliari	AFM059yd6	(CA)n	D6S262	6
cagliari	AFM079zb7	(CA)n	D6S264	6
cagliari	AFM163xa1	(CA)n	D6S279	6
cagliari	CRI-L1065	MspI	D6S21	6
milou	CPHD2	PCR	IGF2R	6
milou	cCI6-105	MspI	D6S191	6
milou	cCI6-105	TaqI	D6S191	6
milou	cCI6-11.1	MspI	D6S141	6
milou	cCI6-119	PvuII	D6S195	6
milou	cCI6-19	MspI	D6S146	6
milou	cCI6-19	TaqI	D6S146	6
milou	cCI6-24	PvuII	D6S149	6
milou	cCI6-31	TaqI	D6S151	6
milou	cCI6-4.1	MspI	D6S136	6
milou	cCI6-41	MspI	D6S157	6
milou	cCI6-41	PvuII	D6S157	6
milou	cCI6-55	TaqI	D6S166	6
milou	cCI6-78.1	MspI	D6S178	6
milou	cCI6-78.1	RsaI	D6S178	6
milou	cCI6-78.1	TaqI	D6S178	6
milou	cCI6-8	PstI	D6S140	6
milou	cCI6-87	RsaI	D6S184	6
milou	cCI6-89	BglII	D6S185	6
milou	cCI6-91	RsaI	D6S186	6
milou	cCI6-91	TaqI	D6S186	6
milou	cCI6-99	PstI	D6S190	6
groningen	AFM248ta5	(CA)n	D7S524	7
marburg	00220/221	HinfI	CFTR	7
marburg	0054/0055	PCR	COL1A2	7
marburg	0056/0057	SCRFI	D7S23	7
marburg	126C1	(GT)n	D7S1494	7
marburg	126F5	(CA)n	D7S1491	7
marburg	127B9	(CA)n	D7S1492	7
marburg	127E2	(CA)n	D7S1495	7
marburg	127E8	(CA)n	D7S1493	7
marburg	127F4	(CA)n	D7S1496	7
marburg	222-223	(CA)n	D7S440	7
marburg	288/289	(AACT)n	D7S460	7
marburg	290-291	(CA)n	D7S461	7
marburg	292-293	(CA)n	D7S462	7
marburg	296-297	(CA)n	D7S466	7
marburg	360/361	(CA)n	EGFR	7
marburg	362-363	(CA)n	D7S435	7
marburg	7pF/7pR	(CA)n	D7S547	7
marburg	AFM074xg5x	(CA)n	D7S483	7
marburg	AFM087yd01	(CA)n	D7S484	7
marburg	AFM098xg9x	(CA)n	D7S486	7
marburg	AFM162xa7	(CA)n	D7S493	7
marburg	AFM168xc3	(CA)n	D7S495	7
marburg	AFM199vh8	(CA)n	D7S502	7
marburg	AFM200wc7	(CA)n	D7S506	7
marburg	AFM217yc5	(CA)n	D7S513	7

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
marburg	AFM220xc01	(CA)n	D7S515	7
bouchet	CEB51	HinfI	D7S596	7
edinburgh	exon3	ApaI1	PDGFA	7
edinburgh	ivs4	ApaI1	PDGFA	7
bouchet	14C13	HaeIII	D7S450	7
bouchet	14C2	HinfI	D7S22	7
bouchet	CEB13	PvuII	D7S467	7
bouchet	CEB16	HaeIII	D7S468	7
bouchet	CEB24	HaeIII	D7S595	7
bouchet	CEB56	HaeIII	D7S598	7
bouchet	CEB81	HaeIII	D7S597	7
mrchbgu	Elastin	PCR	ELN	7
mrchbgu	SIB124A	PvuII	MUC3	7
mrchbgu	SIB124B	PvuII	MUC3	7
cagliari	CW1	Taq_1	D8S9	8
bouchet	CEB22	HaeIII	D8S211	8
bouchet	CEB45	HaeIII	CEB45	8
bouchet	CEB91	HaeIII	D8S356	8
bouchet	CEB35	HinfI	D8S357	8
bouchet	CEB42	HaeIII	D8S358	8
bouchet	CEB6	HaeIII	D8S139	8
cork	WIS_2A	enzyme	WIS_2A	8
cambridge	L256	pcr	D9S749	9
mrchbgu	ABO	DGGE	ABO	9
mrchbgu	EFD126	Msp1	D9S11	9
mrchbgu	AFM073yb11	(CA)n	D9S158	9
mrchbgu	AFM087yd3	(CA)n	D9S161	9
mrchbgu	15.5/6	(CA)n	D9S297	9
mrchbgu	AFM224zh10	(CA)n	D9S175	9
mrchbgu	F2F5	(CA)n	D9S298	9
cambridge	9CMP3-f	(CA)n	D9S143	9
cambridge	9CMP4-b	(CA)n	D9S144	9
cambridge	D9S180	(CA)n	D9S180	9
cambridge	D9S197	(CA)n	D9S197	9
cambridge	G318	(CA)n	D9S283	9
cambridge	g347	(CA)n	D9S287	9
bouchet	CEB23	HaeIII	D9S134	9
bouchet	CEB43	HaeIII	D9S207	9
cambridge	9CMP1	(CA)n	D9S109	9
cambridge	9CMP2	(CA)n	D9S127	9
cambridge	D9S53m	(CA)n	D9S53	9
cambridge	LAMP92	TaqI	D9S29	9
mrchbgu	ABO	(CA)n	ABO	9
mrchbgu	ASSg4	(CA)n	ASS	9
mrchbgu	C7	(CA)n	D9S123	9
mrchbgu	DBH4	(CA)n	DBH	9
mrchbgu	p33.1	HinfI	D9S49	9
mrchbgu	pAbl	PCR	ABL	9
crete	AFM023xc3	(CA)n	D10S186	10
crete	AFM155zc3	(CA)n	D10S201	10
crete	AFM186xe5	(CA)n	D10S210	10
crete	AFM065yh11	(CA)n	D10S190	10
crete	AFM066xa1	(CA)n	D10S191	10
crete	Mfd150	(CA)n	D10S109	10
crete	ZNF22	(CA)n	ZNF22	10
crete	phP450j	XmnI	CYP2E	10
crete	AFM063xf4	(CA)n	D10S189	10
crete	AFM119xh12	(CA)n	D10S197	10
crete	Mfd164	(CA)n	D10S111	10
crete	Mfd28	(CA)n	D10S89	10
crete	VNTR	Taq1	D10S33	10
crete	c10gt01	(CA)n	GLUDP5	10
crete	cMS614	TaqI	D10S92	10
crete	cMS622	Taq_1	D10S90	10
crete	wis5	RsaI	D10S179	10
bouchet	CEB25	HaeIII	D10S180	10

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
bouchet	CEB36	HaeIII	D10S473	10
bouchet	CEB46	HaeIII	D10S471	10
bouchet	CEB7	HaeIII	D10S112	10
bouchet	CEB90	HinfI	D10S472	10
cambridge	W1T1-1	enzyme	D10S102	10
cambridge	W302T8-3	enzyme	D10S102	10
cambridge	p1,2_PCT	enzyme	D10S170	10
cambridge	retT3-1	enzyme	RET	10
cambridge	ret_T7	enzyme	RET	10
cambridge	vac_b	TaqI	ANX8	10
crete	AFM094tc9	(CA)n	D10S192	10
crete	AFM198zb4	(CA)n	D10S212	10
crete	AFM240xa9	(CA)n	D10S220	10
crete	D10S141	(CA)n	D10S141	10
crete	c10gt02	(CA)n	D10S608	10
crete	c10gt03	(CA)n	GLUDP2	10
mrchbgu	TYR5	pcr	TYR	11
bouchet	CEB18	HaeIII	D11S868	11
bouchet	CEB41	HaeIII	D11S1000	11
mrchbgu	JER58A	PvuII	MUC5	11
mrchbgu	JER58B	PvuII	MUC5	11
leiden	26BH1	(CA)n	D11S1383	11
barcelona	AFM026tb5	(CA)n	D12S77	12
barcelona	AFM026tf3	(CA)n	D12S78	12
barcelona	AFM067yc5	(CA)n	D12S79	12
barcelona	AFM107xc11	(CA)n	D12S82	12
barcelona	AFM116xb8	(CA)n	D12S84	12
barcelona	AFM135xe3	(CA)n	D12S87	12
barcelona	AFM206ze5	(CA)n	D12S94	12
barcelona	AFM207ve1	(CA)n	D12S95	12
barcelona	AFM210zd6	(CA)n	D12S97	12
barcelona	AFM262zd9	(CA)n	D12S106	12
barcelona	AFM112yf4	(CA)n	D12S83	12
barcelona	PLA-2	(CA)n	PLA2A	12
barcelona	VWfII-3	TCTA	F8VWF	12
barcelona	mfd84	(CA)n	D12S43	12
milou	M758B6-1	(CA)n	D12S401	12
milou	M758B6-21	(CA)n	D12S400	12
bouchet	16C18	HaeIII	D12S55	12
bouchet	CEB40	HaeIII	25A2/2	12
bouchet	CEB86	HinfI	D12S273	12
marys	PLA_2	pcr	PLA2A	12
marys	mfd_133	(CA)n	D12S63	12
marys	mfd_73	(CA)n	D12S58	12
bouchet	CEB5	HaeIII	D13S107	13
bouchet	CEB69	HinfI	D13S234	13
bouchet	CEB70	HinfI	D13S235	13
groningen	AFM135xb8	(CA)n	D13S158	13
groningen	AFM205wg3	(CA)n	D13S166	13
groningen	AFM248wc1	(CA)n	D13S221	13
groningen	AFM261yg5	(CA)n	D13S173	13
groningen	BER1	(CA)n	D13S147	13
groningen	BER9	(CA)n	D13S146	13
groningen	CU13/1832	(CA)n	D13S134	13
groningen	E1SD/I1SD	BamHI	RB1	13
groningen	L3/L4	(CA)n	D13S231	13
groningen	RB1.20	(CTTT(T))n	RB1	13
groningen	RB1.PCR1	XbaI	RB1	13
groningen	RB1.PCR2	Tth111I	RB1	13
groningen	ca001(A)	(CA)n	D13S128	13
groningen	ca010	(CA)n	D13S137	13
groningen	mfd44	(CA)n	D13S71	13
groningen	mgg14	(CA)n	D13S201	13
groningen	mgg15	(CA)n	D13S319	13
aarhus	Gamma_2	TaqI	WARS	14
roma	AFM210zh4	(CA)n	D14S74	14

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
roma	AFM214yg5	(CA)n	D14S75	14
roma	AFM260xb1	(CA)n	D14S81	14
roma	Fr7-74	PstI	D14S14	14
roma	Mfd42	(CA)n	D14S34	14
roma	X58705	(CA)n	D14S45	14
roma	AFM058yh2	(CA)n	D14S63	14
roma	p18.1	BglII	D14S31	14
roma	AFM242xa9	(CA)n	D14S80	14
roma	AFM199zf4	(CA)n	D14S72	14
bouchet	CEB78	HinfI	D14S13	14
roma	pACE3.4	TaqI	AACT	14
cagliari	Gem-152	MspI	Gem-152	15
cork	AFM112xa1	(CA)n	D15S118	15
cork	AFM164zc9	(CA)n	D15S120	15
milou	AFM218yf12	(CA)n	D15S126	15
aarhus	pAPN1	BclI	ANPEP	15
bouchet	CEB27	HaeIII	D15S105	15
cork	pTD3-21	enzyme	D15S10	15
milou	AFM016yg1	(CA)n	D15S143	15
milou	AFM070xd7	(CA)n	D15S146	15
milou	AFM150xf4	(CA)n	D15S119	15
milou	AFM205ye1	(CA)n	D15S123	15
milou	AFM218yf12	(CA)n	D15S126	15
milou	AFM261xb9	(CA)n	D15S161	15
milou	AFM265xf9	(CA)n	D15S132	15
milou	M770F4	(CA)n	D15S221	15
milou	MH22	(AAAT)13	D15S172	15
milou	THBS-ca	(CA)n	THBS	15
milou	ZI-280	(CA)n	D15S129	15
milou	fibrillin	(TAAAA)n	FBN1	15
milou	formin	HincII	FMN	15
mrchbgu	189-1	TaqI	D15S13	15
mrchbgu	3-21	TaqI	D15S10	15
mrchbgu	pCMW1a	TaqI	D15S24	15
aarhus	PER11	BamHI	DPEP1	16
mrchbgu	313F9	EcoRI	313F9	16
bouchet	14C19	HaeIII	D16S282	16
bouchet	CEB50	HaeIII	D16S307	16
bouchet	CEB58	HaeIII	D16S456	16
bouchet	MS637	HaeIII/HinfI	D16S307	16
lisboa	AFM113xe3	(CA)n	D16S407	16
lisboa	AFM137xf8	(CA)n	D16S408	16
lisboa	AFM238xb2	(CA)n	D16S420	16
lisboa	AFM249yc5	(CA)N	D16S423	16
lisboa	3'HVR	MspI	D16S85	16
lisboa	p79-2-23	TaqI	D16S7	16
lisboa	pEKMDA2.1	TaqI	D16S83	16
aarhus	Beta2_I	EcoRI	APOH	17
aarhus	Beta2_I	PvuII	APOH	17
cagliari	Gem-321	TaqI	Gem-321	17
madrid	AFM044xg3	(CA)n	D17S784	17
madrid	AFM049xc1	(CA)n	D17S785	17
madrid	AFM051xd10	(CA)n	D17S786	17
madrid	AFM168xd12	(CA)n	D17S794	17
madrid	AFM179xg11	(CA)n	D17S798	17
madrid	AFM192yh2	(CA)n	D17S799	17
madrid	AFM234td2	(CA)n	D17S806	17
milou	mfd15	(CA)n	D17S250	17
milou	mfd188	(CA)n	D17S579	17
bouchet	16C17	HaeIII	D17S450	17
bouchet	CEB49	HaeIII	D17S885	17
bouchet	CEB53	HaeIII	CEB53	17
bouchet	CEB84-85	HaeIII	D17S886	17
bouchet	CEB72	PvuII	D17S888	17
bouchet	CEB79	HinfI	D17S889	17
bouchet	MS638	HinfI	D17S26	17

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
edinburgh	AFM020tf12	(CA)n	D18S52	18
edinburgh	AFM036ya1	(CA)n	D18S53	18
edinburgh	AFM123ya1	(CA)n	D18S56	18
edinburgh	AFM147yg7	(CA)n	D18S57	18
edinburgh	AFM164xe3	(CA)n	D18S58	18
edinburgh	AFM178xc3	(CA)n	D18S59	18
edinburgh	AFM178xe3	(CA)n	D18S60	18
edinburgh	AFM193yf8	(CA)n	D18S61	18
edinburgh	AFM197xh12	(CA)n	D18S62	18
edinburgh	AFM240vh6	(CA)n	D18S65	18
edinburgh	AFM240xc7	(CA)n	D18S66	18
edinburgh	AFM248te1	(CA)n	D18S67	18
edinburgh	AFM254vd5	(CA)n	D18S70	18
edinburgh	c102H11021	(CA)n	D18S37	18
edinburgh	cu18005	(CA)n	D18S44	18
caerdydd	pBB2.7	EcoRI	DM	19
caerdydd	AFM224ye9	(CA)n	D19S221	19
aarhus	puPAR2A	PstI	PLAUR	19
aarhus	puPAR2B	PstI	PLAUR	19
bouchet	CEB21	HaeIII	D19S203	19
caerdydd	APOC1	HpaI	APOC1	19
caerdydd	D10	PvuII	D19S63	19
caerdydd	D19S190	(CA)n	D19S190	19
caerdydd	D8	HindIII	D19S62	19
caerdydd	DM-CTG	(CA)n	DM	19
caerdydd	HH71/72	HinfI	DM	19
caerdydd	HH71/89	BpmI	DM	19
caerdydd	M23B	PCR	D19S101	19
caerdydd	pBB2.7	PvuII	DM	19
mrchbgu	B6.7	HinfI	B6.7	20
bouchet	CEB2	HinfI	D20S33	20
bouchet	CEB39	HinfI	D20S136	20
bouchet	CEB57	HinfI	D20S137	20
pasteur	AFM102xa7	(CA)n	D20S104	20
pasteur	AFM120xc7	(CA)n	D20S186	20
pasteur	IP20M61	(CA)n		20
pasteur	AFM046xf6	(CA)n	D20S171	20
pasteur	AFM163yh8	(CA)n	D20S108	20
pasteur	AFM210vb4	(CA)n	D20S114	20
pasteur	AFM142xh4	(CA)n	D20S107	20
pasteur	AFM029yc3	(CA)n	D20S96	20
pasteur	AFM044xb4	(CA)n	D20S98	20
pasteur	AFM057xa3	(CA)n	D20S100	20
pasteur	AFM077xd3	(CA)n	D20S103	20
pasteur	AFM058xa1	(CA)n	D20S101	20
pasteur	AFM080ya1	(CA)n	D20S211	20
pasteur	AFM123yf8	(CA)n	D20S106	20
pasteur	AFM190xg1	(CA)n	D20S111	20
pasteur	AFM123xh12	(CA)n	D20S105	20
pasteur	AFM066xh3	(CA)n	D20S102	20
pasteur	AFM036ya3	(CA)n	D20S97	20
pasteur	AFM051xf12	(CA)n	D20S99	20
pasteur	AFM205th8	(CA)n	D20S113	20
pasteur	IP20M05	(CA)n	D20S64	20
pasteur	IP20M62	(CA)n	D20S42	20
pasteur	IP20M77	(CA)n	D20S46	20
pasteur	IP20M03	(CA)n	D20S55	20
pasteur	IP20M57	(CA)n	D20S41	20
pasteur	IP20M12	(CA)n	D20S48	20
pasteur	IP20M48	(CA)n	D20S52	20
pasteur	IP20M83	(CA)n	D20S45	20
pasteur	IP20M17	(CA)n	D20S59	20
pasteur	IP20M07	(CA)n	D20S57	20
pasteur	IP20M06	(CA)n	D20S56	20
pasteur	IP20M28	(CA)n	D20S63	20
pasteur	IP20M71	(CA)n	D20S44	20

Table 1. (continued)

Lab	Probe	Enzyme	Symbol	Ch.
pasteur	IP20M43	(CA)n	D20S40	20
pasteur	IP20M41	(CA)n	D20S39	20
marys	D21S156	(CA)n	D21S156	21
milou	AFM-M266e10-1	(CA)n	D21S1266	21
milou	AFM-M815h10-9	(CA)n	D21S1268	21
barcelona	abmc13	(CA)n	D21S368	21
barcelona	abmc15	(CA)n	D21S369	21
barcelona	abmc19	(CA)n	D21S416	21
barcelona	abmc2	(CA)n	D21S364	21
barcelona	abmc21	(CA)n	D21S414	21
barcelona	abmc23	(CA)n	D21S1421	21
barcelona	abmc27	(CA)n	D21S415	21
barcelona	abmc28	(CA)n	D21S409	21
barcelona	abmc29	(CA)n	D21S1261	21
barcelona	abmc3	(CA)n	D21S366	21
barcelona	abmc33	(CA)n	D21S1419	21
barcelona	abmc37b	(CA)n	D21S1234	21
barcelona	abmc52	(CA)n	D21S406	21
barcelona	abmc53	(CA)n	D21S408	21
barcelona	abmc57	(CA)n	D21S1264	21
barcelona	abmc6	(CA)n	D21S365	21
barcelona	abmc60	(CA)n	D21S1224	21
barcelona	abmc65	(CA)n	D21S409	21
barcelona	abmc7	(CA)n	D21S367	21
barcelona	abmc75	(CA)n	D21S1235	21
barcelona	abmc82	(CA)n	D21S1262	21
bouchet	CEB17	HaeIII	D22S267	22
bouchet	CEB31	HaeIII	D22S266	22
bouchet	CEB47	HaeIII	D22S408	22
bouchet	CEB59	HinfI	D22F101S1	22
bouchet	CEB68	HinfI	D22S409	22
aarhus	AFM105xc5	(CA)n	DXS984	X
aarhus	AFM248we5	(CA)n	DXS1001	X
aarhus	pMS613	PstI	DXS438	X
cambridge	AFM212xe5	pcr	DXS996	X
edinburgh	AFM136yc7	(CA)n	DXS990	X
leiden	AFM234yf12	(CA)n	DXS999	X
aarhus	L754	PstI	DXS84	X
aarhus	MAOA	(CA)n	MAOA	X
aarhus	PDHa	(CA)n	PDHA1	X
aarhus	PDHb	(CA)n	PDHA1	X
aarhus	PDHc	(CA)n	PDHA1	X
cagliari	Gem-129	MspI	Gem-129	X
bouchet	29C1	HaeIII/PvuII	DXYS14	X
bouchet	CEB12	PvuII	DXYS14	X
bouchet	CEB29	HaeIII	DXYS90	X
bouchet	MS600	HinfI	DXYS78	X
bouchet	MS639	HinfI	DXYS89	X

R. Kumar-Singh[a]
H. Wang[a]
B. Carritt[b]
T.A. Kruse[c]
T.V. McCarthy[d]
G. Vergnaud[e,f]
P. Humphries[a]

The EUROGEM Map of Human Chromosome 1

[a] Wellcome Ocular Genetics Unit, Department of Genetics, Trinity College, Ireland;
[b] MRC Human Biochemical Genetics Unit, University College London, UK;
[c] Institute of Human Genetics, University of Aarhus, Denmark;
[d] Department of Biochemistry, University College Cork, Ireland;
[e] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[f] Centre d'Études du Bouchet, Vert le Petit, France

The framework linkage map of chromosome 1 produced in this study is composed of 42 markers spaced at an average distance of 7.8 cM. All of these markers are based on simple sequence repeats and are hence amenable to amplification using PCR. The total sex-averaged, male and female lengths of the chromosome are estimated at 322.8 cM, 230.6 cM and 425.3 cM respectively. This may be compared to the recently published maps from Généthon which are 292 cM (sex-averaged), 218 cM (male) and 362 cM (female), while the CHLC map has a sex-averaged length of 384 cM. The framework map was constructed with a stringency of odds exceeding 1000:1 for a marker to be included. Of a total of 36 markers which make up the framework map, data for the markers D1S236, D1S173, D1S33, D1S339, D1S104 and D1S249 have been derived specifically from this study. The other markers typed in this study of chromosome 1, namely D1S153, D1S172, D1F101S2, D1S338, CEB98, AT3, D1S103, S100A7, D1F35S2 and PGD have not been included in the framework map as they could not be placed with odds exceeding 1000:1. This map will greatly facilitate the localisation of disease-causing genes on this chromosome and will aid in the development of the physical map of chromosome 1.

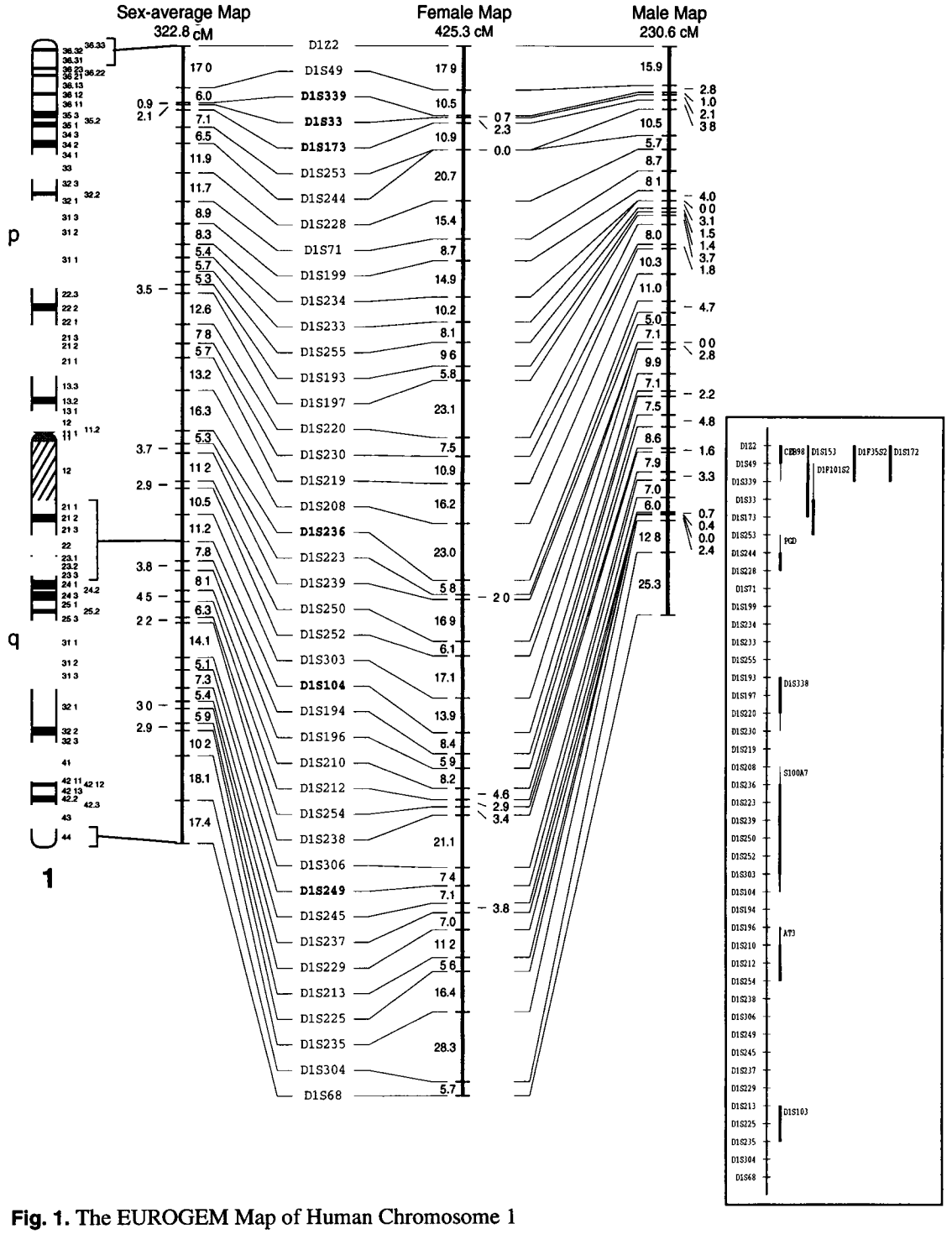

Fig. 1. The EUROGEM Map of Human Chromosome 1

T.J. Flint[a]
J.M. Hertz[a]
G. Vergnaud[b,f]
S. Orrù[e]
C.B. Harvey[c]
B. Bakker[d]
T.A. Kruse[a]

The EUROGEM Map of Human Chromosome 2

[a] Institute of Human Genetics, University of Aarhus, Denmark;
[b] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[c] MRC Human Biochemical Genetics Unit, University College London, UK;
[d] Department of Human Genetics, Leiden University, 2300 RA Leiden, The Netherlands;
[e] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy;
[f] Centre d'Études du Bouchet, Vert le Petit, France

For the chromosome 2 map, 157 markers from the CEPH database (version 6) and 20 markers analysed in the EUROGEM project were included in the map construction. An initial map was constructed using the 'build' option of the CRI-MAP package with odds of 10,000:1 as inclusion limit. The 'flips' facility of CRI-MAP was used and only markers that could be positioned unambiguously with odds better than 1000:1 were kept on the map. From this map a second round of 'build' calculations were carried out with odds of 1000:1 as the limit for inclusion of additional loci, followed by a second round of 'flips' calculations. As the quality of the map (order and distance) is very sensitive to errors in the raw data, a number of error checking steps were included: all the markers were checked for allelic exclusion, non-Mendelian inheritance, intralocus recombinations using 'chrompic' and doubtful marker typings were identified and rechecked by the laboratory submitting the data. All the markers were then tested for map expansion associated with their introduction into the map. Five loci demonstrated map expansion of more than 5 cM indicating potential typing errors seen as false recombinants. These markers were excluded from the map.

The resulting map contains 49 loci from 2p25 to 2q37.3 spanning a genetic distance of 343.5 cM (sex- averaged).

In 1992, three chromosome 2 maps with loci ordered with odds better than 1000:1 were published: The CEPH-consortium map [6] containing 36 loci, the NIH/CEPH map [7] with 36 loci and the Généthon map [2] containing 45 short tandem repeat (STR) markers. The map presented here contains 23, 33 and 36 loci, respectively, which were not ordered unambiguously in the 1992 maps. Recently, three more chromosome 2 maps have been published: a MultiMap-map [8] contains 45 loci, CHLC-map [4] containing 64 loci including 40 STR-markers and a Généthon-map [3] containing 97 STR-markers. Compared to these maps, the map presented here contains 29 loci not in the CHLC-map, and 41 loci not in the MultiMap-map. Compared to these six maps, we only find discrepancy with respect to the order of loci in one case. On distal 2q we have located D2S125 more distal than D2S140, whereas in the Généthon 1992 map, this order is reversed. In the very recent Généthon 1994 map, this order is the same as the one presented here.

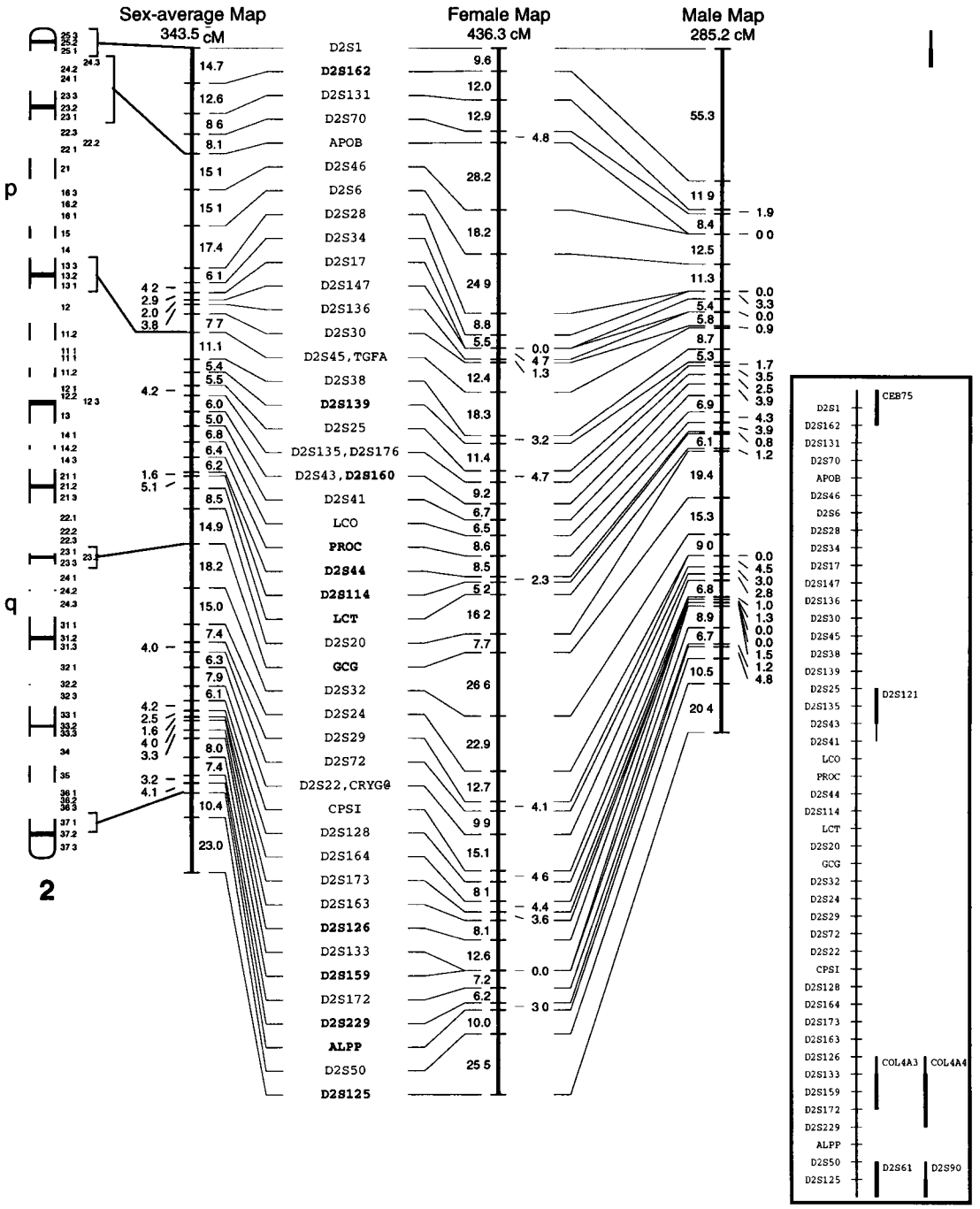

Fig. 2. The EUROGEM Map of Human Chromosome 2

M. Schürmann[a]
B. Müller[b]
C. Duvigneau[a]
J. Leutelt[a]
S. Krey[a]
R. Kumar-Singh[c]
M. Lush[d]
D. M. Swallow[e]
G. Vergnaud[f,g]
E. Bakker[h]
E. Schwinger[a]
A. Gal[a]

The EUROGEM Map of Human Chromosome 3

[a] Institut für Humangenetik, Medizinische Universität zu Lübeck, FRG;
[b] Abteilung für Pädiatrische Genetik, Kinderpoliklinik, LMU München, FRG;
[c] Wellcome Ocular Genetics Unit, Department of Genetics, Trinity College, Ireland;
[d] Department of Pathology, Cambridge University, UK;
[e] MRC Human Biochemical Genetics Unit, University College London, UK;
[f] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[g] Centre d'Études du Bouchet, Vert le Petit, France;
[h] Department of Human Genetics, Leiden University, 2300 RA, Leiden, The Netherlands

The chromosome 3 map consists of 30 loci spanning a sex-averaged length of 260.7 cM. The sex-specific lengths in our map are 226.7 cM in males and 306.8 cM in females. These values are quite similar to those obtained by other groups for chromosome 3 with sex-averaged lengths of 235 [2], 233 [9], 249 [10], and 269 cM [11]. However, our map is considerably shorter than those based on mainly RFLP typing, for example the NIH/CEPH consortium (334 cM) [7].

The average genetic distance between adjacent loci is 8.7 cM. Of the 29 intervals defined by the map, ten are larger than 10 cM, two of them being larger than 15 cM, and there is a single gap of 25 cM (between D3S1282 and SST). Also the distances between the loci are similar to those reported by other groups. In two cases, the intervals calculated by us were considerably shorter than those given in the CHLC (D3S196-D3S1279: 7.6 vs 11.3 cM) [4] and Généthon (D3S1275-D3S1282: 8.8 vs 14 cM) [3] map, respectively.

In constructing the map, we used RFLPs from the CEPH database (version 6) as anchor loci wherever possible in order to combine information on "old" and "new" markers at the same time. The order of loci has been established by an odds ratio criterion of (greater than) 1000:1 using 'flips4' within CRI-MAP. Several of the loci included have not been genetically mapped previously, e.g. D3S621, D3S1038, D3S1475, D3S1476, D3S1447, D3S1448, D3S1449, D3S1450, HRG, MUC4, SI and RBP1. Other markers, such as ACPP, RHO, D3S1261, D3S1262, D3S1263, D3S1265, D3S1271, D3S1277, D3S1279, D3S1282, D3S1300, D3S1303, SST and D3S1297, have been genotyped on an increased number of CEPH families. However, using our data set, some of the loci could not be placed in a single interval with an odds ratio of (greater than) 1000:1 and a broader assignment spanning two adjacent intervals is given in the map. Nevertheless, independent information obtained by genetic or physical mapping can be used to localise these loci. For example, a single recombination in a total of 362 informative meioses places D3S1475 distal of D3S1476 (Buard and Vergnaud, unpublished). Similarly, while RHO could not be mapped by us genetically relative to D3S1273 and ACPP, a chromosomal inversion localizes RHO proximal to these latter loci. Many of the loci on 3q have been mapped physically by somatic cell hybrids [12] carrying only part of chromosome 3 with defined cytogenetic breakpoints (cen - D3S1271 - BP3q12 - D3S1281 - BP3q13.2 --- D3S1267 - BP3q21 - D3S1273 --- D3S1275 - BP3q25.2 - D3S1282 - BP3q26.2 - SST - 3qter). This information allows a limited alignment of the cytogenetic and linkage map of chromosome 3q.

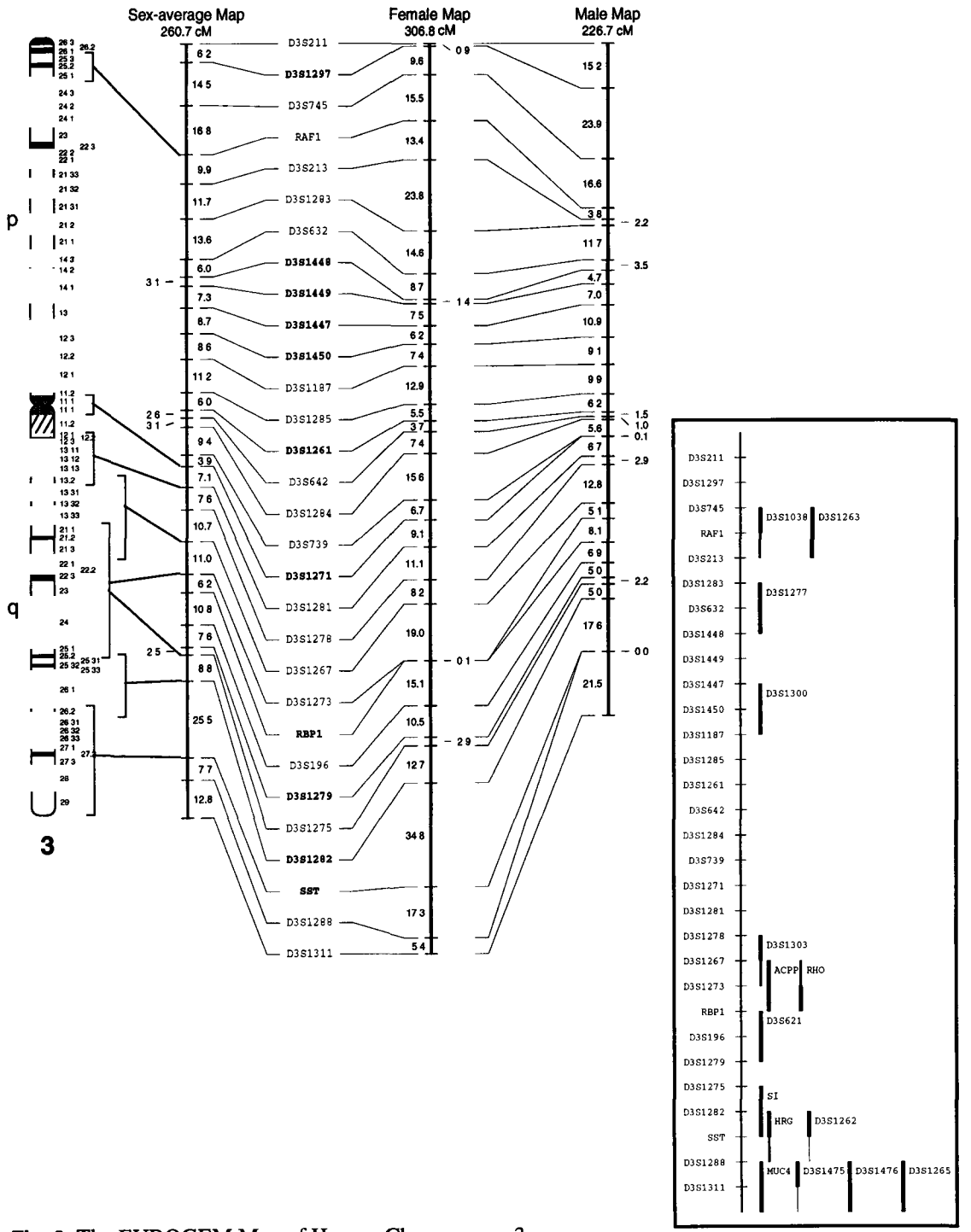

Fig. 3. The EUROGEM Map of Human Chromosome 3

E. Bakker[a]
R.H.A.M. Vossen[a]
B.P. Riley[b]
R. Sherrington[c]
G. Vergnaud[d,e]
N.M. Pearson[a]

The EUROGEM Map of Human Chromosome 4

[a] Department of Human Genetics, Leiden University, 2300 RA Leiden, The Netherlands;
[b] Department of Biochemistry, St. Mary's Hospital Medical School, London, UK;
[c] Department of Molecular Psychiatry, University College London, UK;
[d] Centre d'Études du Bouchet, Vert le Petit, France;
[e] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France

During the first phase of the EUROGEM genetic mapping project 22 polymorphic loci on chromosome 4 were typed, 18 by the Leiden group, 2 by the French group (GV) and 1 by each of the UK groups (BPR and Sue Povey). Of the 22 loci 15, were CA-repeat markers, including 5 AFM (Généthon) markers, 3 were VNTR's and 4 were RFLP's. Both the (CA)n and the VNTR markers were tested on DNA samples of all individuals of the 40 CEPH pedigrees. The RFLP markers were typed on ready made Southern blots, provided by the CEPH resource centre, containing digested DNA's of individuals from 20 selected CEPH pedigrees. In total, some 10,000 genotypings were performed. All genotype information was rigorously error checked by hand and entered into the GENBASE program. A second check was made by running the LINK2SUM program to test for inconsistencies in the data (allelic exclusion and non-paternity). All possible errors were verified and either corrected or the conflicting genotype was deleted from the dataset before submission to the CEPH.

In the CEPH version 6 database, there are 241 markers, representing more then 155 loci. Not all of these loci are typed on all 40 CEPH pedigrees (e.g. the Généthon markers have been typed on 8 pedigrees) and some do not give many informative meioses. Some data are present in multiple copies due to previous haplotyping efforts.

For 11 of the 22 markers typed in the EUROGEM project there were already some data in the CEPH database. In our linkage and CRI-MAP effort, these systems were replaced with new updated and corrected genotyping data. From the database, all systems were checked for their information content (numbers of individuals tested and number of informative meioses). In total, 25 systems could be haplotyped. In 13, no intralocus recombinants occurred. However, in the remaining 12 loci, intralocus cross-overs were detected. Therefore we chose to include only the most informative systems in our CRI-MAP building effort.

A first CRI-MAP 'build' (1000:1) was attempted on all the selected data. For the 13 haplotyped systems, the recombination fraction was forced to zero. The outcome from the first 'build' was a 60 locus map, which seemed not to be very stable at the telomeres. On this raw 60 locus map subsequent 'flips2' runs were performed each time deleting the conflicting loci. When the map appeared stable at 'flips2' a 'flips4' run was used to verify the stability. This resulted in a relatively small 17 loci map, which was used as a baseline. We then attempted to fit, one by one, some of the loci deleted earlier using the original 60 locus 'build' as a reference. The best supported loci were retained in the stable map, expanding the map to a total of 36 loci at a 10 cM average genetic distance.

In total, 16 (D4S125, D4S127, DRD5, D4S403, D4S405, D4S174, GABRA2, D4S398, D4S406, FABP2, D4S192, D4S243, D4S112, D4S408, D4S171, D4F35S1) of the 22 markers tested by the EUROGEM labs were inserted into this 1000:1 supported framework map, while the other 6 (D4S43, D4S1100, D4S129, GABRB1, LR12, D4S14) were regionally localised within well-defined intervals. The framework map generated also includes 20 loci taken from the CEPH database. In total the map contains an order of at least 1000:1 for 36 loci, 24 being highly polymorphic (CA)n markers, 3 being haplotypes of multiple systems. The total map length is now estimated to be 283.7 cM. Thus a < 10 cM average map density is reached. There are 3 gaps >15 cM present in this map. These gaps also are found in previously published genetic maps [8]. Therefore one could speculate on the presence of recombination hotspots or areas which are not very polymorphic.

Our future effort in the second phase of the EUROGEM project will be directed towards gap filling and reaching an average map distance of 3-5 cM. A second aim will be to localise expressed sequences on the map and come to a more integrated genetic, gene and physical map.

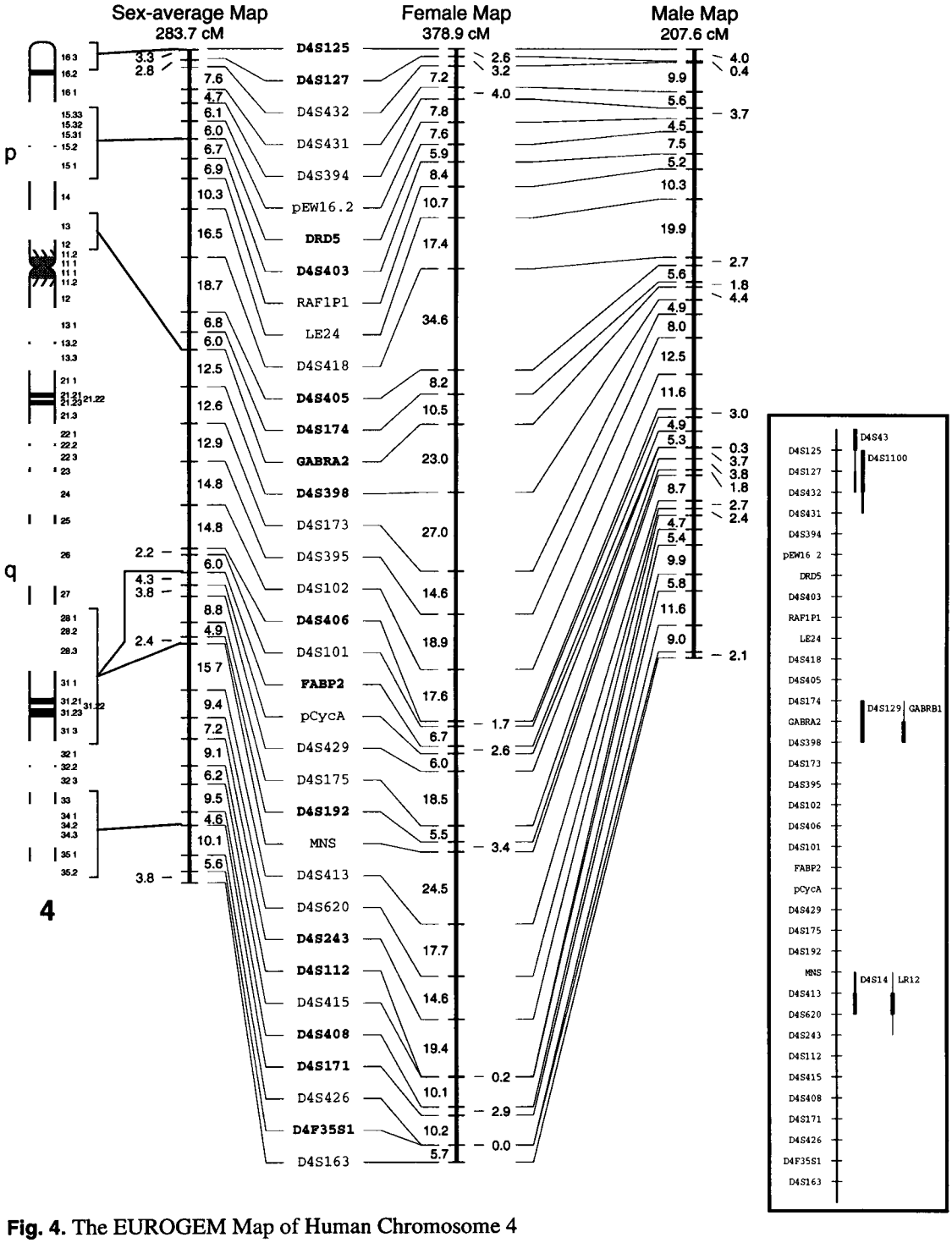

Fig. 4. The EUROGEM Map of Human Chromosome 4

The EUROGEM Map of Human Chromosome 5

M. Villamar[a]
B. Gomendio[a]
E. Perera[a]
D. Telleria[a]
C. Fizames[b]
J.L. San Millan[a]
J. Weissenbach[b]
J.J. Schott[c]
M. Dixon[e]
M. Hollyoake[f]
F. Moreno[a]

[a] Unidad de Genética Molecular, Hospital Ramón y Cajal, 28034 Madrid, Spain;
[b] Généthon, Evry, France;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Centre d'Études du Bouchet, Vert le Petit, France;
[e] Department of Cell and Structural Biology, University of Manchester, UK;
[f] MRC Human Biochemical Genetics Unit, University College London, UK

An initial map of chromosome 5 was prepared by Dr. Moreno and colleagues. Each member of the 40 CEPH reference families was genotyped with 54 DNA markers using standard procedures. The RFLP at loci D5S6, D5S63 and D5S39 were determined using membranes supplied by Resource Centre 1 (CEPH), and CA-repeats were genotyped using a multiplex approach [13]. In addition, all of the individuals from eight families (102, 884, 1331, 1332, 1347, 1362, 1413 and 1416) were also typed for 14 markers by a second method. The amplification products of a single microsatellite from each individual were run separately in non-denaturing polyacrylamide gels, stained with ethidium bromide, and photographed. Of a total of 1890 genotypings, only 11 were found to be discrepant.

All the data were analysed with the diagnostic software programs used by Gyapay and colleagues [3] to detect genotyping errors and false double recombinants. Several hundred genotypings, involving different individuals and markers, were repeated to verify the data. Genotypes appearing as double recombinants after several rounds of verification were kept for construction of the map. It is possible that some of these recombinants result from unmasked mutation or conversion of a marker.

Using the MultiMap program, 49 microsatellite markers could be ordered with odds above 1000:1 against alternative orders. The PIC values of these ordered markers ranged from 0.47 to 0.91, 32 of them showing PIC above 0.7. Thirty-nine are Généthon markers included in the Gyapay et al. map [3], six (D5S208, D5S268, D5S260, D5S204, D5S107 and D5S346) are anonymous markers selected from the literature, D5S1356 was isolated from a non-chimaeric 380 kb YAC mapping to 5q13, at the centromeric side of the SMA (spinal muscular atrophy) locus, and two are genes, HMGCR and IL9. These genes have been mapped to bands 5q13.3-q14 and 5q22.3-q31.3. The markers that could not be unambiguously ordered showed PIC values between 0.34 and 0.6, and two of them D5S6 and D5S63, are contained in the YAC used to isolate D5S1356. D5S39 is closely linked to the SMA locus, on the distal side.

A total of 32 mutations, affecting 22 microsatellites, were observed in 39,600 genotypings, the mutation rate (8×10^{-5}) being close to that observed by others [14]. The mutations were either duplications or deletions of one or two CA repeats. Finally we would like to emphasise the importance of error correction and its effect on the genetic map length. Prior to the removal of false recombinants our map was 17% longer.

In this initial map, the female and male maps spanned 284.8 and 174.5 cM repectively, and the sex-averaged map was 227.4 cM. The order of Généthon markers, deduced from the study of only 8 families, was confirmed with odds greater than 1000:1 in every case. In addition, the map extendend the Généthon map by 26cM [3]. Visual comparison of both maps indicated that both the introduction of new markers and the analysis of 4-fold more meioses were responsible for the 13% expansion of the map.

An additional fifteen markers submitted by two other EUROGEM laboratories were placed in unique positions using CRI-MAP with the 'all' option. This gave a final sex-averaged map of 236.6 cM in length.

GABRA1 was uniquely positioned as the most distal marker on the long arm but was left out of the framework map because it added more than 45 cM to the total length, which suggested possible typing errors.

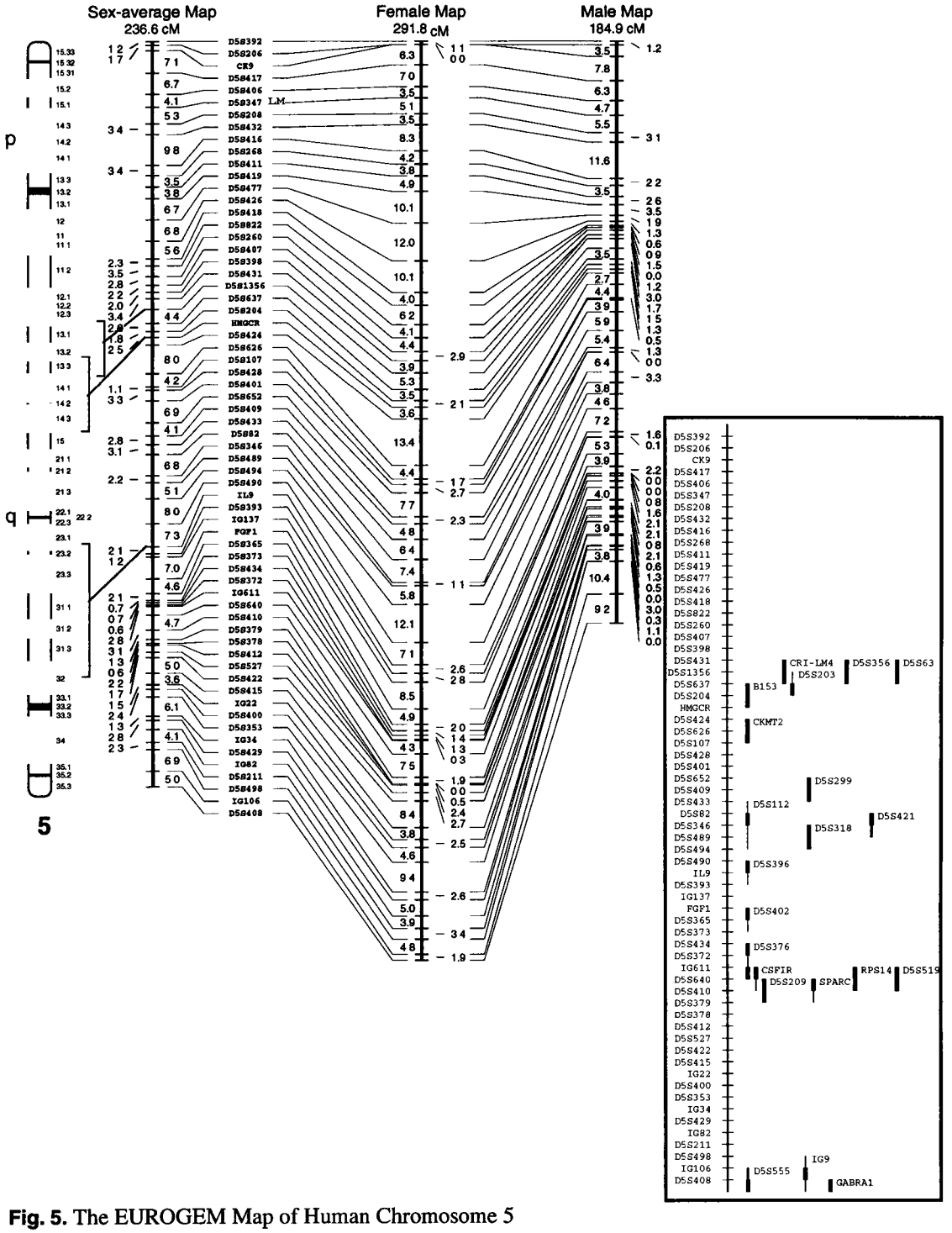

Fig. 5. The EUROGEM Map of Human Chromosome 5

The EUROGEM Map of Human Chromosome 6

L. Terrenato[a]
C. Jodice[a]
P. Blas[a]
A. Loizedda[b]
L. Contu[b]
J. Buard[d]
G. Vergnaud[c,d]
P. Humphries[e]
R. Kumar-Singh[e]
C. Massart[f]
H. Cann[f]

[a] Dipartimento di Biologia, Università "Tor Vergata", 00133, Roma, Italy;
[b] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Centre d'Études du Bouchet, Vert le Petit, France;
[e] Wellcome Ocular Genetics Unit, Department of Genetics, University of Dublin, Ireland;
[f] Fondation Jean Dausset - CEPH, Paris, France

Within the EUROGEM project, genotypes from 50 chromosome 6 markers were studied. For map construction, markers D6S143, D6S177, D6S178 (RsaI), D6S178 (TaqI), D6S186 (TaqI) and D6S188 were exluced as they contained no informative meioses; markers D6S191 (MspI and TaqI), D6S146 (MspI and TaqI), D6S157 (MspI and PvuII) were haplotyped. Therefore, 41 markers with informative data were available. The CRI-MAP package was used for analysis. In a series of preliminary runs, these markers were inserted into a framework map made of 30 CHLC markers [11]. The preliminary map, containing 71 markers, was considered useful for identifying possible errors even though it was not significantly supported. The 'chrompic' procedure identified double recombinants in very small regions and 61 typing errors were suggested. Following rechecking, the datafile was corrected accordingly. It was decided to maximize the probability of including EUROGEM markers on the map. The building procedure for the final version of the map used 8 markers chosen from the CHLC map as landmarks. They are D6S344 (6p24), D6S29 (6p21.3), D6ZI (6cen), D6S251 (6q14- q16.2), D6S252 (6q14-q16.2), D6S278 (6q16.3-q21), D6S255 (6q25.2), D6S48 (6q27). A threshold of a maximum of 270 cM for the entire chromosome (sex-averaged) was chosen [8,15]. It was assumed that a higher value would indicate that typing errors were still present in the datafile leading to increased recombination frequency and therefore inflation of map distance.

The EUROGEM map of chromosome 6 is a 32 point map containing 36 marker loci, each positioned with local support of at least 1000:1. The map includes the original 8 landmark loci, 14 newly mapped EUROGEM markers and 10 loci that were re-mapped with already existing genotypes and/or genotypes determined in the EUROGEM program. The average observed heterozygote frequency of the 36 mapped markers is 68%. Twenty markers are highly polymorphic (observed hetozygote frequency above 70%).

Thirteen additional markers could not be placed on the map with the accepted support criterion. Each of these was localized to a likely location with respect to the map. These markers were SCA1, C4A, D6S171, D6S137, D6S162, D6S271, D6S190, D6S140, D6S141, D6S195, D6S166, D6S191 and D6S149. There were three cases of intragenic recombination: for PIM this was due to genotypes obtained with different probes, while for D6S37 and D6S146, due to genotypes determined with different restriction enzymes. The genetic map is inconsistent with the consensus physical map of 6p23 [16]. On the genetic map D6S289 is mapped telomeric to D6S260 while it is centromeric to D6S260 on the physical map. Accurate rechecking of all the relevant genotypes has confirmed a single recombinant, carried by CEPH panel individual 134411, between D6S289 and D6S260, which results in the telomeric location of D6S289. The analysis of other markers in this region is probably necessary to solve these contradictory results. For an evaluation of the effectiveness of the EUROGEM project, it should be noted that the two recently published genome maps [8,4] contain 33 and 53 markers, respectively, on chromosome 6, with only 17 in common, and therefore a total of 69 markers have been mapped with local support of at least 1000:1. The EUROGEM map adds 18 new markers mapped with the usual support criterion, for a total of 87, an increase of 26%. A genetic map of chromosome 6 containing 87 markers covering about 270 cM (average interval distance of 3 cM) can probably be constructed once residual typing errors are removed. So far, attempts to insert more than 40 markers into the map have consistently increased the genetic length of chromosome 6 to above the acceptable threshold of about 270 cM.

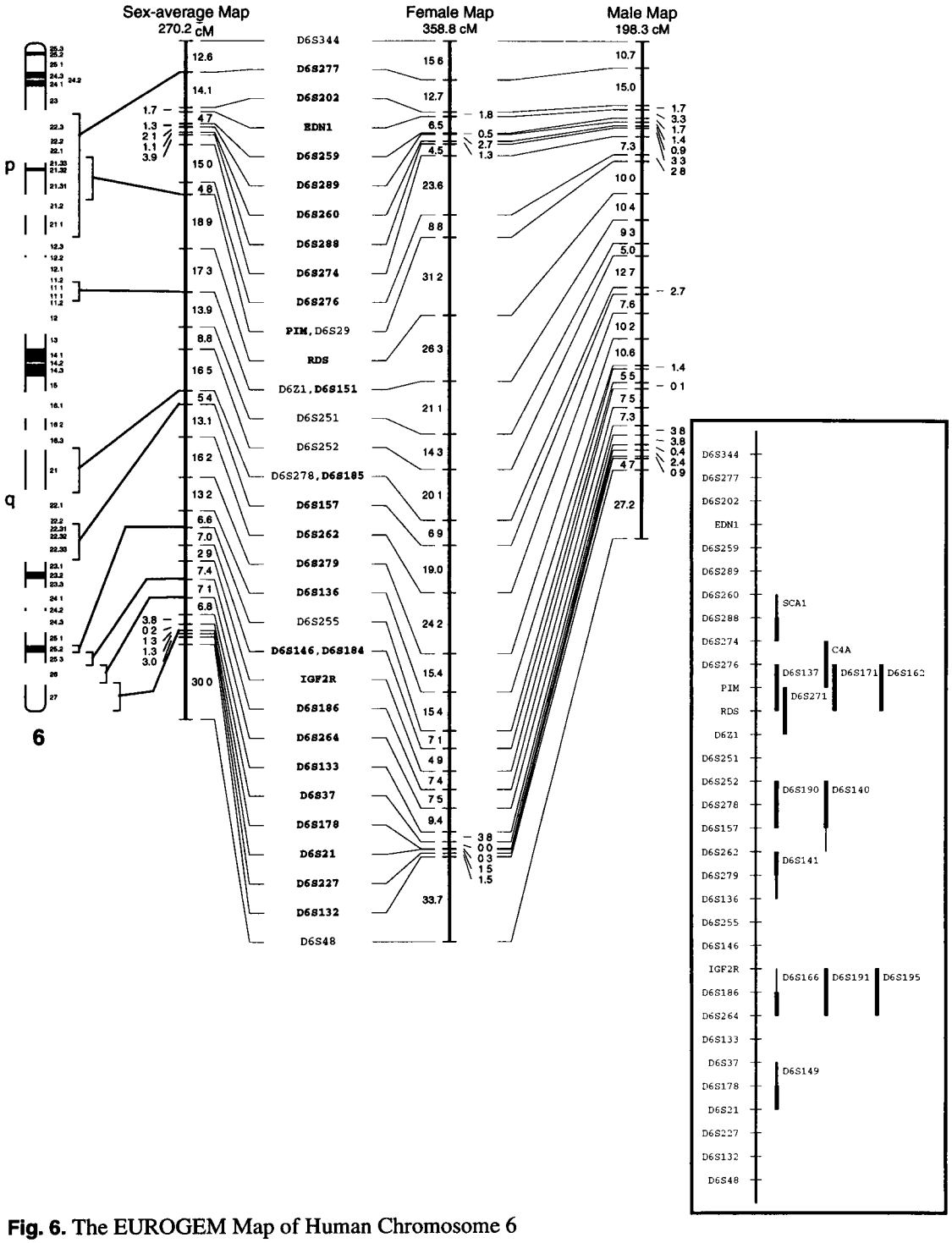

Fig. 6. The EUROGEM Map of Human Chromosome 6

THE EUROGEM Map of Human Chromosome 7

F. Badbanchi[a]
M. Otto[a]
U. Kohlhauer[a]
N. Grzeschik[a]
S. Beck[a]
S.J.L. Smith[g]
D. M. Swallow[b]
R.F. Kooy[c]
G. Vergnaud[d,f]
M. Aldred[e]
K-H. Grzeschik[a]

[a] Med. Zentrum Für Humangenetik, Marburg, FRG;
[b] MRC Human Biochemical Genetics Unit, University College London, UK;
[c] Department of Medical Genetics, University of Groningen, The Netherlands;
[d] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[e] MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK;
[f] Centre d'Études du Bouchet, Vert le Petit, France;
[g] Human Genetics Unit, Department of Medicine, University of Edinburgh, UK

The first NIH-CEPH consortium map was based mainly on anonymous RFLP markers and functional genes [17]. Provisional index maps presented at the First International Workshop on Chromosome 7 Mapping 1993, by two groups, attempted to integrate a number of the first generation microsatellite markers [2], typed on 8 of the CEPH families, with other PCR-based markers like EGFR, GCK or TCRB, MUC3, ERV3, TCRG, and IL6 [17,18].

The EUROGEM map is exclusively based on 30 markers for which new data were generated by genotyping of the 40 CEPH families. It includes 10 Généthon markers, other microsatellites and RFLP markers, selected by the Resource Centre or the consortium, and 5 new dinucleotide microsatellite markers identified in Marburg: D7S1491, D7S1492, D7S1493, D7S1494, D7S1495. Details on the markers used to build the map can be obtained from the Genome Data Base (GDB).

All genotype information was error-checked visually and entered into the GENBASE program. A second check was made by running the LINK2SUM program to test for inconsistencies in the data (allelic exclusion and non-paternity). All possible errors were verified by retyping and either corrected or the conflicting genotype was deleted from the dataset before inclusion into the study. The analyses for map building were carried out using CRI-MAP, starting from the order predicted by the Généthon markers published by Weissenbach et al. [2], and including the additional markers in a stepwise fashion. For marker systems typed in the EUROGEM project for which there was already some data present in the CEPH version 6 database, in our map building effort this information was overruled by our new data. A first preliminary CRI-MAP 'build' was attempted on all newly genotyped markers and selected markers from the CEPH database. Markers at odds of <1000:1 were excluded. Local support for the preliminary map was assessed using the CRI-MAP options 'flips2' and 'flips4'. Subsequently all non-EUROGEM markers were eliminated.

The resulting EUROGEM map shown in the figure is a baseline map of 30 markers (out of 40 typed by the EUROGEM labs) for which new information was available ordered in unique positions with odds of at least 1000:1. The order of markers which had also been used by other groups agrees well with the one published previously [17,2]. In particular, the order in 7q36 (cen - D7S468 - D7S22 - tel) which seemed to be inverted in the map of Hill et al. [18] (cen - D7S22 - D7S468 - tel) is back to the order indicated by Helms et al. [17] and Gurreri et al. [19], probably due to the availabilty of new data in the present study. The map is 268.3 cM (sex-averaged), 337.4 cM (female), and 209.3 cM (male) in length. Physical locations had been described for 5 of the loci mapped in our study. In addition, we assigned the 5 microsatellite markers developed in our group by FISH and analysis of a somatic cell hybrid panel (data not shown) to regions of chromosome 7. As a result, 10 of the 30 markers on the genetic map have a well-defined physical position allowing the integration of genetic and physical maps: PDGFA - 7p22; D7S1495 - 7p22; D7S1492 - 7p22; D7S513 - 7p21; D7S484 - 7p14 to p15; D7S506 - 7p11.2; MUC3 - 7q22; D7S1493 - 7q22; D7S1494 - 7q36; D7S1491 - 7q36. Several important disease loci have been mapped to chromosome 7 recently: Split hand/split foot malformation (SHFD1) to 7q21-7q22; a deletion breakpoint interval in 7q22 in myeloid disorder; Williams-Beuren-Syndrome (WBS) to 7q11.23; two retinitis pigmentosa genes on 7q and 7p; a "complex bilateral polysyndactyly"-gene and a gene for triphalangeal thumb, both to the 7q36 region; a gene for holoprosencephaly to 7q36, and a gene for Saethre-Chotzen-type of craniosynostosis to distal chromosome 7p.

The integration of the markers on the genetic maps of this chromosome into physical maps and contiguous collections of clones during the next round of EUROGEM will define the position of these genes more precisely and thus speed up their identification.

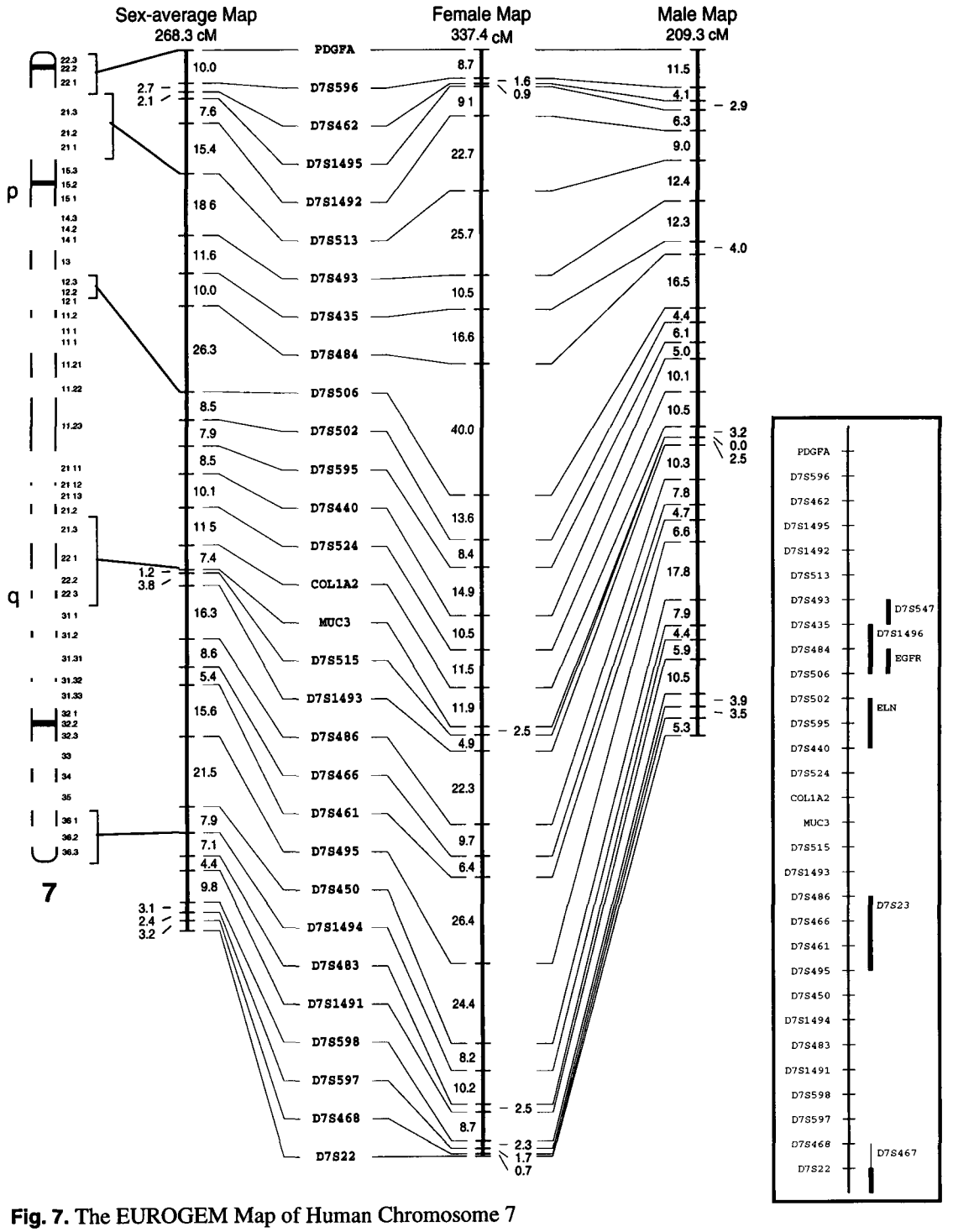

Fig. 7. The EUROGEM Map of Human Chromosome 7

S.A. Cox[a]
N.K. Spurr[a]
G. Vergnaud[b,c]
L. Contu[d]
C. Carcassi[d]
T. McCarthy[e]

The EUROGEM Map of Human Chromosome 8

[a] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), South Mimms, Hertfordshire, UK;
[b] Centre d'Etudes du Bouchet, Vert le Petit, France;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy;
[e] Department of Biochemistry, University College, Cork, Ireland

During the first phase of the EUROGEM genetic mapping project, 8 polymorphic marker systems detecting 8 loci on chromosome 8 were typed. None of the markers typed were (CA)n repeat markers.

The genotype data was submitted to the anonymous ftp server ftp.gene.ucl.ac.uk in CEPH text format. LINK2SUM was used to check the data for allelic exclusions. One marker was found to contain allelic exclusions and the originator was asked to check their data.

Previously, a CRI-MAP framework map of chromosome 8 had been built using an error-checked CEPH version 6 database. This error checked database is available by anonymous ftp at gc.bcm.tmc.edu in the directory /public/daiger. The files are called consort8.lib and consort8.dat. This map contained 80 markers from 61 loci and the order was supported by 1000:1 at 'flips5'. The length of the female and male maps was 299.4 cM and 164.8 cM respectively, which is very close to the lengths of the recent CHLC maps [4].

The 'all' option of CRI-MAP [5] was used to fit the 8 EUROGEM markers in this previously constructed map. The 'chrompic' option of CRI-MAP was run on the resulting map. A few intralocus recombinants were detected and removed. Contributors were asked to check other potential errors in genotypes detected by 'chrompic'.

The locus order of the updated map was checked with 'flips2'. Stepwise removal of loci was continued until the order was supported by odds of 1000:1. The new order of loci was checked with 'chrompic' and no further errors were found. The order of the markers was supported by odds of 1000:1 when it was checked with 'flips4'.

The map contains 60 loci, five of which are from EUROGEM and 19 from Généthon. All the EUROGEM maps are approximately 16 cM shorter than the CHLC maps. The female and male maps are 274 cM and 149 cM respectively. The difference in map lengths may be due to the extensive error checking carried out on both the EUROGEM and the CEPH consortium chromosome 8 databases. It is interesting to note that the male map is almost half the length of the female map. This is consistent with previously published genetic maps of chromosome 8.

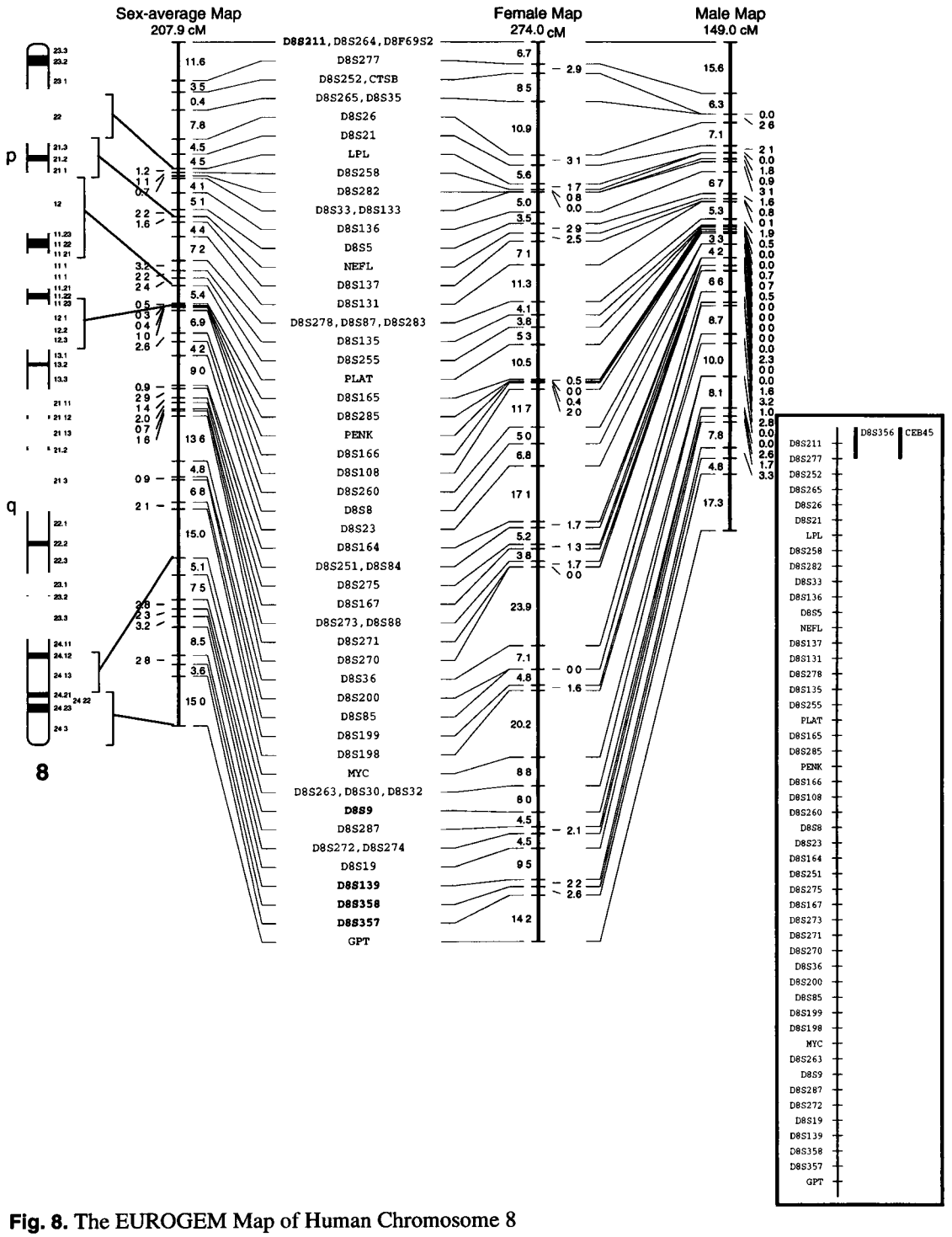

Fig. 8. The EUROGEM Map of Human Chromosome 8

J. Attwood[a]
G. Vergnaud[b,d]
M.L. Lush[c]
D.C. Rubinsztein[c]
D. Goudie[c]
M. Ferguson-Smith[c]
S. Povey[a]

The EUROGEM Map of Human Chromosome 9

[a] MRC Human Biochemical Genetics Unit, University College London, UK;
[b] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[c] Cambridge University, Department of Pathology, Cambridge, UK;
[d] Centre d'Études du Bouchet, Vert le Petit, France

A framework map was constructed using corrected data from the CEPH Consortium map [20] and selecting a set of well-spaced markers whose order was beyond reasonable doubt [21]. The framework used was supported by CRI-MAP 'flips' option at odds of at least 10,000:1. After removal of intralocus recombinants, the EUROGEM markers were submitted to CRI-MAP in decreasing order of informativeness to be built into the framework map. Généthon markers were made into haplotyped systems (hap_sys0) with their CEPH counterparts but, otherwise, EUROGEM markers replaced duplicate systems in the framework map. After each 'build' run, the result was tested with 'flips2' and markers not supported were removed. When no more markers could be added, the remaining markers were temporarily inserted in their most likely positions and 'chrompic' output generated. This was examined for double recombinants in short distances and single recombinants clustered in families. Suspicious data were rechecked by the contributing laboratory and the map rebuilt. The final order was found to be supported at odds of at least 1000:1 by four-way 'flips'.

26 loci on chromosome 9 have been typed by the EUROGEM collaboration and 18 of these have been fitted into the map. The male genetic map of chromosome 9 has been estimated as 116 cM by direct observation of chiasmata (data of M. Hulten, reported in [22]). Most published genetic maps of chromosome 9 are longer than this. For example, the distance from D9S54 to D9S11 in males has been estimated as 183.9 cM [4] and 162.3 cM (CEPH Consortium map, [20]). Recent index marker maps are shorter overall [23], 129 cM and [3], 121 cM but these are confined to PCR-able markers and are not strictly comparable.

The map presented here has a length of 149 cM in males and is similar in length to the Généthon map [3], in the region in which they can be compared (D9S168 - D9S158). There is no absolute centromeric marker but the distance from D9S15, very close to the centromere, to the most distal short arm marker D9S54 is estimated as 50 cM in males, exactly as predicted from the chiasma map. The genetic map is therefore approaching reasonable agreement with the chiasma map (given the limitation of the multipoint methods used). However the genetic maps do not extend to either telomere so rejoicing over this agreement may be premature.

There are three regions of the present map which need further comment. The order of genes in the distal part of 9p is not at all clear and two of the EUROGEM markers typed from this region (D9S143 and D9S749) have not been positioned uniquely in spite of the relatively large distances involved and the highly polymorphic nature of the markers. This may well be related to the difficulty of detecting errors in the markers at the ends of the map.

Several additional markers typed in the 9q22.3 region have not been uniquely positioned on the map, presumably because they lie too close together. However a combination of physical mapping and genetic mapping on non CEPH families reported at the 3rd Workshop on chromosome 9 [24] has suggested the order cen-S12-S197-S180-S109-S29.

At the distal end of 9q an improvement over previous maps has been achieved by the addition of a new minisatellite marker (D9S207), by retyping an 'old' marker, D9S11 on EUROGEM blots and by more extensive typing of Généthon marker D9S158. The estimate of the distance between D9S158 (the most distal microsatellite marker) and D9S11 (the most distal marker) has now been reduced to 2.4 cM in females and 6.8 cM in males.

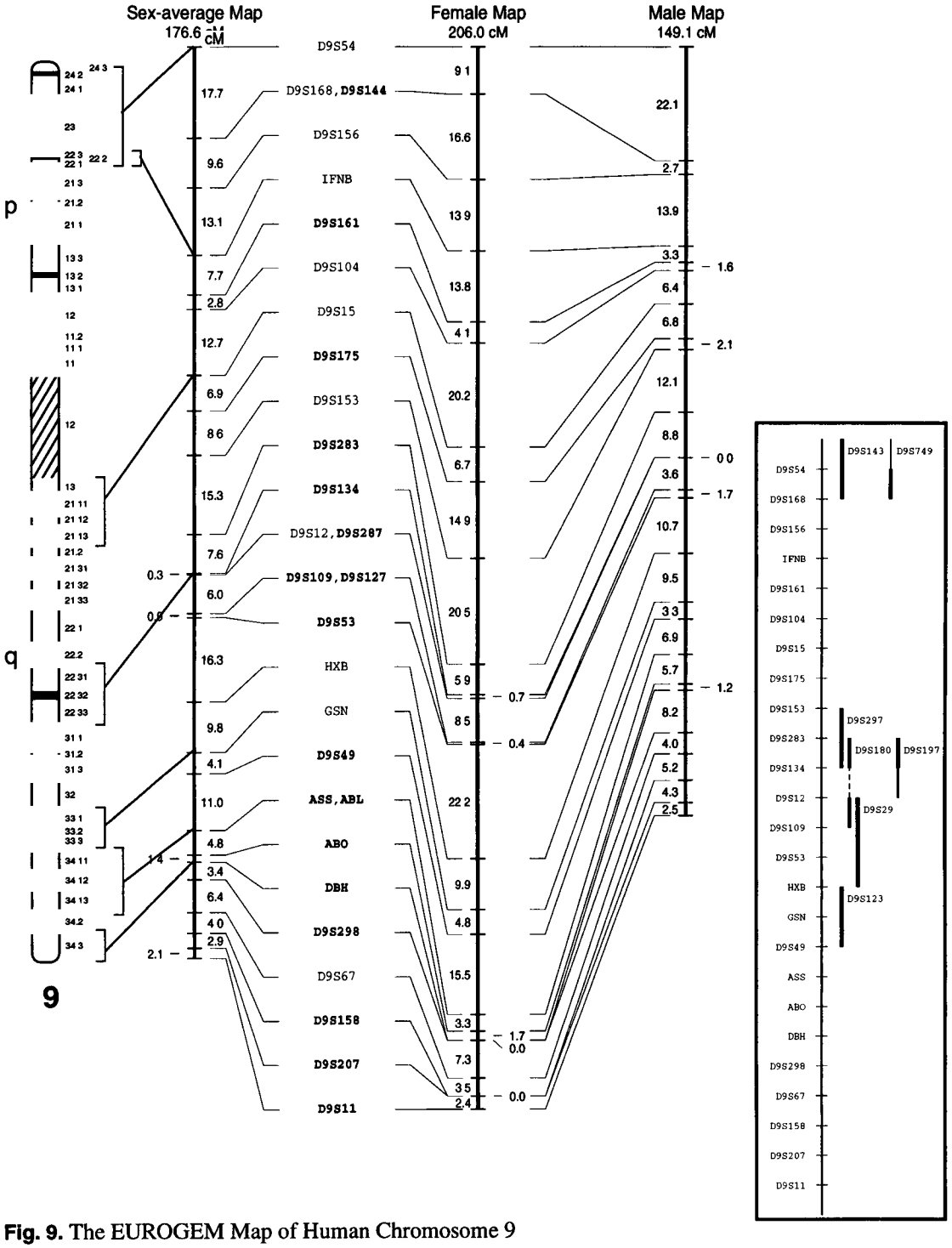

Fig. 9. The EUROGEM Map of Human Chromosome 9

M. Kapsetaki[a]
M. Kokkinaki[b]
D. Angelicheva[a,*]
B. Lubyova[b,*]
H. Mavraki[b,*]
A. Argyrokastritis[a]
G. Vergnaud[c,e]
M. Ferguson-Smith[d]
D.C. Rubinsztein[d]
M. Lush[d]
N. K. Moschonas[a,b]

The EUROGEM Map of Human Chromosome 10

[a] Institute of Molecular Biology and Biotechnology, FORTH-Hellas, Heraklion. Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology
[b] The Department of Biology, University of Crete, P.O. Box 1527, Heraklion 711 10, Crete, Hellas;
[*] Present addresses: Laboratory of Molecular Pathology, University Hospital of Obstetrics and Gynaecology, Sofia, Bulgaria (D.A.); Dept., of Molecular Biology, Comenius University, Mlynska dolina B-2, 842 15 Bratislava, Slovakia (B.L.); Human Genetic Resources, Imperial Cancer Research Fund, Clare Hall Laboratories, Potters Bar, Herts UK) (H.M);
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Cambridge University, Department of Pathology, Cambridge, UK;
[e] Centre d'Études du Bouchet, Vert le Petit, France

Human chromosome 10 is a medium-size sub-metacentric chromosome representing 4.6% of the length of the autosomes. Currently, nearly a hundred genes (i.e. about 2.5% of the expected number), more than 650 DNA segments and about 400 STSs have been assigned to this chromosome [25]. Nearly 20 genetic diseases have been documented to be associated with gene loci mapped to chromosome 10. Interestingly, it has been recently suggested that gene(s) associated with early stages of the development of certain types of cancer, including prostate cancer [26] and glioblastoma multiforme [27] are possibly located at the distal region of 10q.

Our work included the use of highly polymorphic microsatellites and VNTRs for the genotypic analysis of the 40 CEPH family DNAs. To build a comprehensive chromosome 10 map, we combined our genotypic data concerning 19 microsatellite and 8 RFLP markers together with the data for 30 additional markers obtained from the CEPH database version 6. Three of the microsatellite markers were identified at IMBB (Heraklion) by screening several genomic clones containing members of the glutamate dehydrogenase (GLUD) gene family known to map to various chromosome 10 regions [28,29].

Linkage analysis was performed at IMBB by CRI-MAP version 2.4. The map building included sequential integration of markers in an order starting from a pair of markers considered as either the most informative or arbitrarily defined as being in a fixed order using a criterion of 1000:1 odds. For error checking, we used the 'chrompic' option of the program. In most cases potential data errors were checked by retyping. Corrected data were used for recomputing. The construction of a well-supported framework map included the calculation of the local support for every pair of markers in a fixed or a 'flipped' order resulting from the comparison of the respective likelihood values.

Our map contains 24 microsatellite and 20 RFLP highly polymorphic markers (average heterozygosity 0.65) ordered in unique positions with odds >1000:1. The regional positions of 4 additional markers (D10S33, ANX8, RET and CYP2E) have also been determined. The sex-averaged map is 216.6 cM with a mean genetic distance between loci of 4.92 cM. It extends from D10S92 (pter) to D10S6 (qter). The length of the female and the male map is 271.4 cM and 167.7 cM, respectively. Nine markers, GLUD1, GLUDP2, GLUDP5, ZNF22, D10S471, D10S472, D10S473 (GV, unpublished), D10S112 and D10S170 (M F-S, unpublished), have not been previously included in a chromosome 10 genetic linkage map. Quite usefully, our map overlaps at certain regions with other recently constructed maps [25], thus permitting valuable order and distance comparisons. For example, compared to the recent Généthon map [3], we have placed 5 additional loci, i.e. D10S472, D10S473, D10S112, D10S90, and D10S6 distally to D10S212 (10qter). Furthermore, 4 CEPH reference markers, D10S32, D10S34, D10S109 and D10S12, used in the Généthon map, have been placed at unique positions. Eighteen of the markers used have been localised by other techniques, including fluorescent in situ hybridisation (data not shown). The cytogenetic location of these markers correlates well with the proposed order. Accordingly, D10S34, previously mapped to 10p, should be physically located very close to the centromere on 10p. Similarly, D10S4, previously mapped to 10q22.1-23.3, can be localised within 10q23.3. This study will further facilitate the improvement of the physical map of chromosome 10 and contribute to the systematic correlation of disease phenotypes to genes on this chromosome.

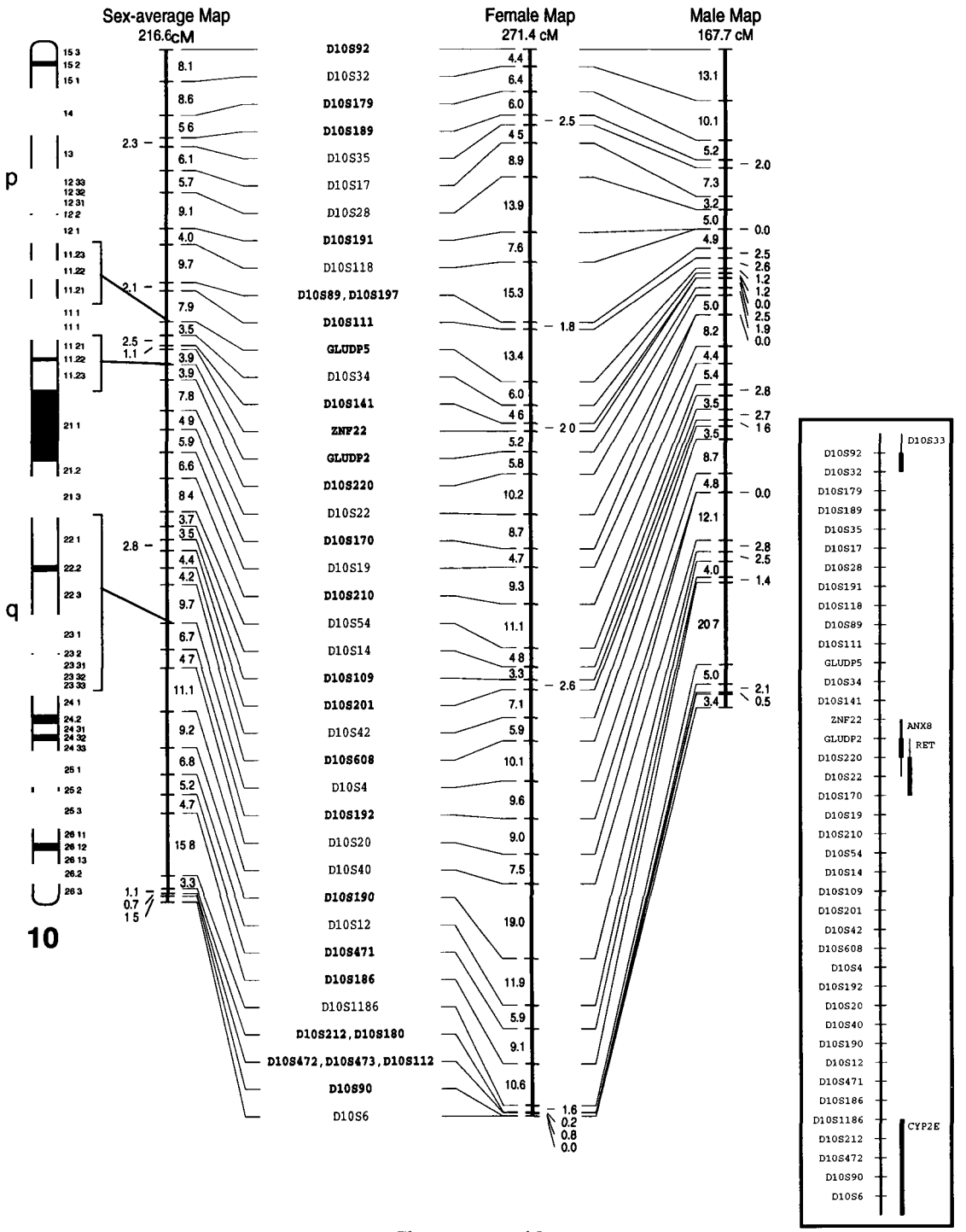

Fig. 10. The EUROGEM Map of Human Chromosome 10

S. Povey[a]
J. Attwood[a]
E. Bakker[b]
D.M. Swallow[a]
G. Vergnaud[c,d]

The EUROGEM Map of Human Chromosome 11

[a] MRC Human Biochemical Genetics Unit, University College London, UK;
[b] Department of Human Genetics, Leiden University, 2300 RA, Leiden, The Netherlands;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Centre d'Études du Bouchet, Vert le Petit, France

A framework map of chromosome 11 was constructed using corrected data from the CEPH Consortium map (M. Litt and P. Kramer, personal communication) and selecting a set of well-spaced markers whose order could be supported at odds of at least 1000:1.

After removal of intralocus recombinants, the EUROGEM markers were submitted to CRI-MAP in decreasing order of informativeness to be built into the framework map. Généthon markers were made into haplotyped systems (hap_sys0) with their CEPH counterparts but, otherwise, EUROGEM markers replaced duplicate systems in the framework map. After each 'build' run, the result was tested with 'flips2' and markers not supported were removed. When no more markers could be added, the remaining markers were temporarily inserted in their most likely positions and 'chrompic' output generated. This was examined for double recombinants in short distances and single recombinants clustered in families. Suspicious data were rechecked by the contributing laboratory and the map rebuilt. The final order was found to be supported at odds of at least 1000:1 by four-way 'flips'.

Only 5 loci (6 polymorphisms) have been typed by the EUROGEM Consortium on chromosome 11. Three of these have been fitted uniquely into the map, which of course relies heavily on the cleaned up database kindly provided by Dr Michael Litt. The ordering of markers has proved most difficult in 11p15.5. One new minisatellite marker (D11S868) has been positioned, but two highly variable markers in this region could only be placed approximately. These two markers, the minisatellite D11S1000 and the mucin gene MUC5 are both very clear and highly informative which should be useful in mapping this region. The only reason for the failure to order them precisely is their very close proximity to D11S922. A single recombinant would suggest that MUC5 is the most distal of these markers. The total length of the genetic map presented here (sex-averaged) is 159.5 cM, the distance from HBB to D11S912 being estimated as 134 cM, rather shorter than the distance between these markers in the CHLC map (163 cM) [4]. The distance from HBB to D11S387 is much reduced in the current map (150 cM) compared with the NIH/CEPH Consortium map [7] where it is estimated at 220 cM.

A feature of chromosome 11 is the number of hybrid breakpoints available to anchor genetic markers to cytogenetic positions. Physical data shown on this map have been taken not only from GDB but also from [30].

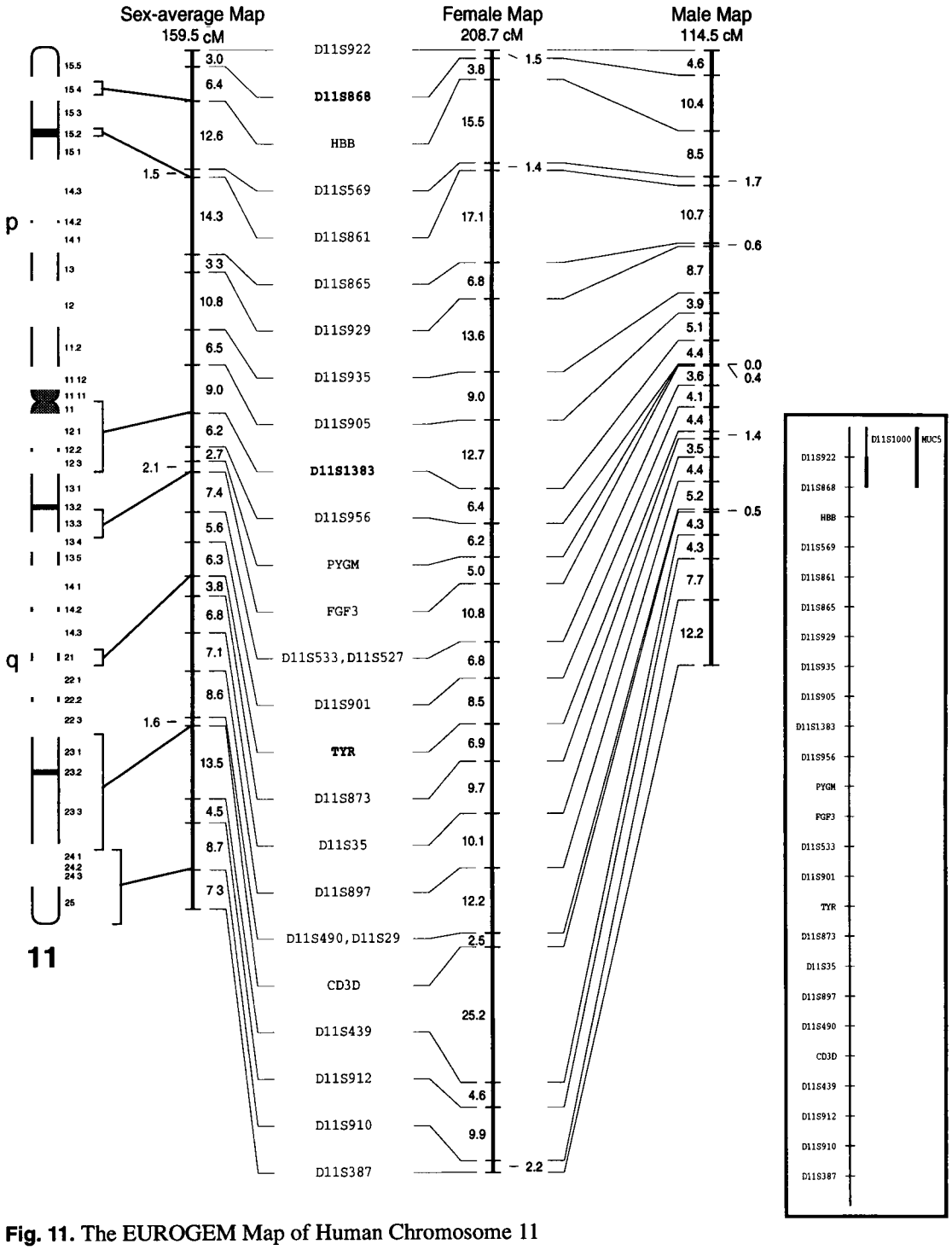

Fig. 11. The EUROGEM Map of Human Chromosome 11

A. Bosch[a,e]
I. Banchs[a,e]
A. Puig[a]
G. Vergnaud[b,c]
V. Allamand[d]
X. Estivill[a]

The EUROGEM Map of Human Chromosome 12

[a] Molecular Genetics Department, Cancer Research Institute, Barcelona, Catalonia, Spain;
[b] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[c] Centre d'Études du Bouchet, Vert le Petit, France;
[d] CEPH/Généthon, Paris, France;
[e] Both authors contributed equally to this work.

Human chromosome 12 is a medium-size submetacentric chromosome that represents 4.7% of the total human genome. At the last chromosome 12 workshop, 147 genes were assigned, but most of them remain uncloned. Chromosome 12 contains the genes responsible for spinocerebellar ataxia type 2 (SCA2), vonWillebrand coagulation factor (VWF), phenylketonuria (PAH), the genes for several metabolic defects, as well as translocations involving various tumours and a specific type of leukaemia [31]. As many genes have not yet been isolated and many others not localised in detail, there is the need to improve the genetic map to facilitate linkage analysis of families affected by hereditary diseases involving this chromosome. More than 100 microsatellites are available on GDB and these are useful tools for building linkage maps. We have genotyped 21 markers (1 trinucleotide, 1 tetranucleotide, 18 dinucleotide repeats and 1 RFLP), with an average heterozygosity of 0.75, in the CEPH reference families under the EUROGEM project, and a genetic map has been constructed using the CRI-MAP program and index markers available from CEPH version 6 and CHLC version 2 genotype databases.

The framework map was built by first constructing three independent yet concordant maps. The first, starting with the most polymorphic pair of markers; the second, starting with the most distal pair at the p arm, and the third starting with the most distal pair of markers at the q arm. All of these pairs of markers had an interlocus distance greater than 10 cM. Beginning with these pairs, all the other markers, ranked in order of informativeness, were subsequently added at odds of at least 1000:1. The consensus map obtained from the combination of these three maps was used to place all the possible remaining loci that could be localised with odds greater than 1000:1. When two or more crossovers were found in each individual meioses using the 'chrompic' option of CRI-MAP, possible genotype errors were checked by regenotyping all the individuals involved and afterwards rerunning 'chrompic'. Further error checking was performed as necessary. However, the high mutation rate of microsatellite loci in lymphoblastoid cell lines poses additional problems when building high resolution chromosome maps [14]. The final linkage map contains 30 markers mapping to 25 uniquely placed loci, with a sex-average length of 195.1 cM. The male and female lengths are 137.9 and 269.8 cM respectively. In the male map, only three intervals are greater than 10 cM. These are located at the centromere (14.2cM) and near both telomeres (20.1 cM at pter and 24 cM at qter). The 24 intervals have an average size of 5.7 cM. Eleven more markers have been approximately placed on the map. Of all the markers included in this map, there were 33 dinucleotides, 3 tetranucleotides, 1 trinucleotide and 4 RFLPs with a total average heterozygosity of 0.71. The genetic location of these markers is consistent with their previously described cytogenetic location and other linkage maps. Most of the EUROGEM typed markers have been analysed in the 40 CEPH reference families, and the length is slightly longer than previously reported linkage maps, which contained genotypes of only 8 families [2,8]. Markers D12S388, D12S389, D12S75, D12S379, 25A2/2 and D12S273 have not previously been localised in a linkage map. The present map has a similar level of resolution and gap lengths as the recently developed maps of [8] and [4]. The newly published map with 92 markers (42 with odds greater than 1000:1) reduced the largest gap to 17 cM [3]. Mapping these new markers in the 40 reference families will allow the construction of a high resolution map of this chromosome.

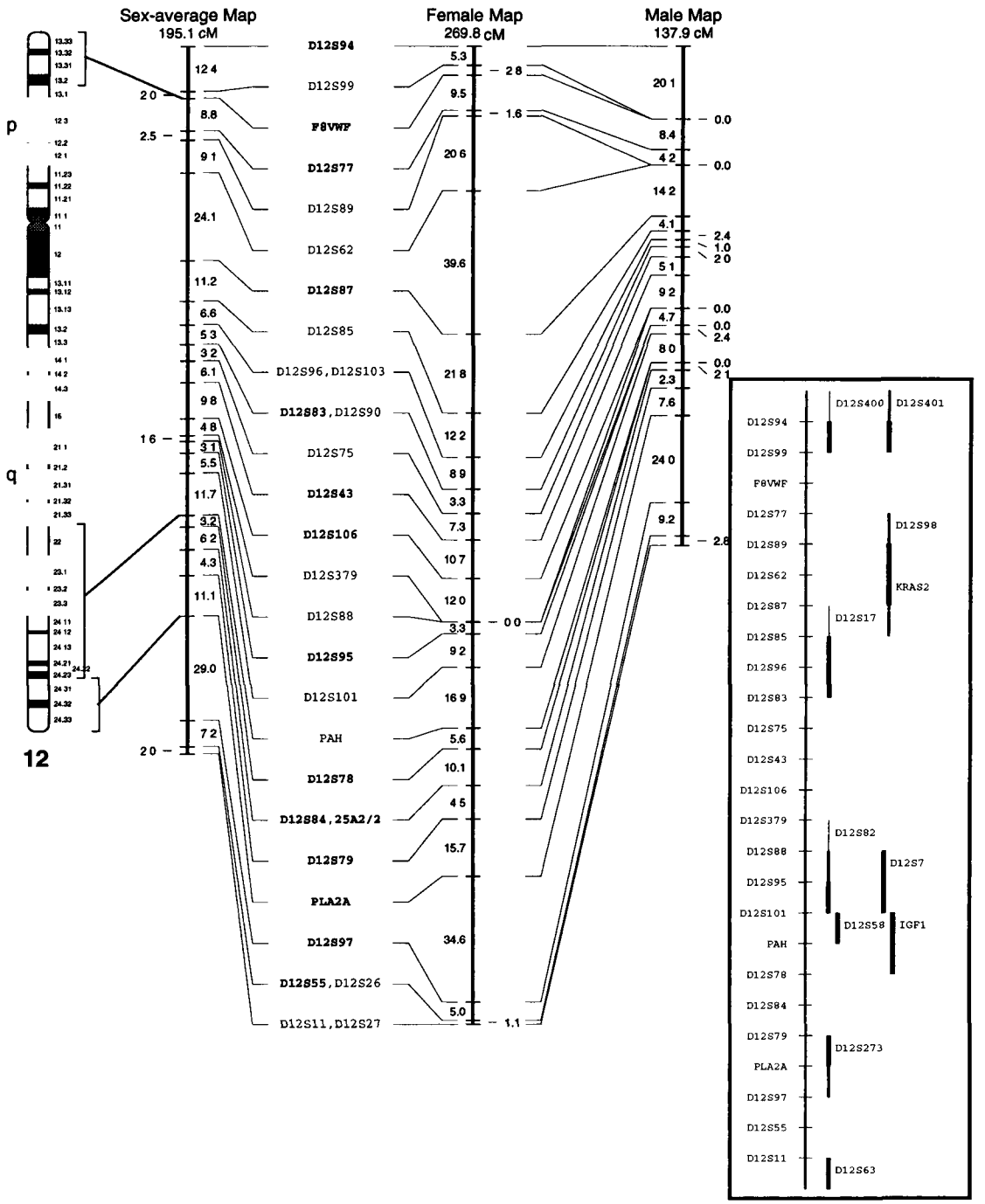

Fig. 12. The EUROGEM Map of Human Chromosome 12. Markers D12S17, IGF1, KRAS2, D12S7 and D12S98 were not typed within EUROGEM.

R.F. Kooy[a]
A. Wijngaard[a]
E. Verlind[a]
G. Vergnaud[b,c]
H. Scheffer[a]
C.H.C.M. Buys[a]

The EUROGEM Map of Human Chromosome 13

[a] Department of Medical Genetics, University of Groningen, The Netherlands;
[b] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[c] Centre d'Études du Bouchet, Vert le Petit, France

Based on the number of chiasmata in cytogenetic counts, chromosome 13 was estimated to have a genetic length of approximately 130 cM (sex-average) [32]. The short arm is believed not to contribute to the genetic length of chromosome 13.

Several genetic maps based on restriction fragment length polymorphisms (RFLPs) have been published. Data on 59 of these markers have been used to construct a CEPH consortium linkage map of chromosome 13 [33], eventually containing 25 uniquely placed loci spanning 178 cM (Kosambi cM, sex-average). Three genetic maps based on microsatellite polymorphisms have been presented [2,34,35], defining 17, 9, and 22 distinct genetic loci, respectively. The maps cover an estimated length of 144 cM, 65 cM and 99 cM, respectively. Except for D13S71, which appears on the maps of [34] and [35], these maps have no markers in common.

In this study 20 markers were typed over a set of 40 CEPH families. The 20 markers included 5 as yet untyped microsatellite markers, namely D13S146, D13S147, D13S201 (RFK, unpublished), D13S231, and D13S319 [36], 7 microsatellite markers that had previously been typed on a subset of 8 families, namely D13S128, D13S134, D13S137 [35], D13S158, D13S166, D13S173, D13S221 [2], one marker, D13S71, included for reference purposes, because it is also present on 2 other microsatellite-based chromosome 13 maps, three telomeric variable number of tandem repeats (VNTR) markers, namely D13S107, D13S234, and D13S235 [52], and 4 intragenic RB1 markers (3 RFLPs and a (CTTT(T))-repeat). In addition to these 20 markers, genotype data on 8 microsatellite and 2 RFLP-based markers, D13Z1 (alphaR1(680)/TaqI), and COL4A1 (the haplotype HT21/XmnI/HaeIII/HinfI/HindIII) were taken from the CEPH database version 6. For the total of 30 markers, an average heterozygosity of 71% (78%, excluding the four RFLP markers) was calculated. The markers for which the order had a level of support of at least 1000:1 odds were selected to build a framework map. This map contained 26 markers at 22 loci. Double recombinants were identified using the 'chrompic' option of CRI-MAP, rechecked on the original autoradiographs, and corrected if necessary. The markers of the framework map have an average spacing of 5.7 cM, and span a total distance of 148.4 cM, with a maximum interval of 17.9 cM between D13S126 and D13S127 on the sex-average map. The mean female to male recombination ratio is 1.46. For the non-telomeric part of the genetic map, here defined as proximal to the marker D13S173, this ratio is 1.71. It is reversed in the telomeric part of the chromosome, between D13S173 and D13S235/D13S107, where it is 0.65. The order of markers has been confirmed by physical mapping to a deletion hybrid panel [34,36] except for the markers distal to D13S128. For the 4 markers that did not fit the criteria used for inclusion in the framework map, a likely location is provided as 'all' output of CRI-MAP. The observed mutation rate for microsatellite markers was 0.13%. A highest mutation rate of 0.7% was observed for the (CTTT(T))-repeat. In previous studies, 3 intragenic RFLP markers in the RB1 gene had been typed by Southern blotting, for which we used PCR followed by restriction endonuclease treatment. Four discrepancies with previously submitted data (CEPH database, version 6) were detected. Those data are likely to comprise typing errors, as the genotypes contained give rise to double recombinants within a short interval. This suggests that, at least for these RFLPs, PCR may be a more accurate way of typing RFLPs than Southern blotting. The map contributes to the generation of a framework map of chromosome 13, with precise physical mapping for five loci, namely D13Z1 at the centromeric region, RB1 at 13q14.2-q14.3, D13S31 (between D13S201 and D13S137) at the junction of bands 13q14.3-q21.1, D13S71 at proximal 13q32, and COL4A1, D13S107, D13S234, and D13S235 at 13q34. The genetic map extends from the centromeric to the telomeric region, but the distance of D13S235/D13S107 to the telomeric end of chromosome 13 is not known. Compared to previous integrated chromosome 13 maps, the largest interval is considerably reduced, the telomeric end is well defined by the VNTR loci, and map distances are smaller, suggesting a lower error rate.

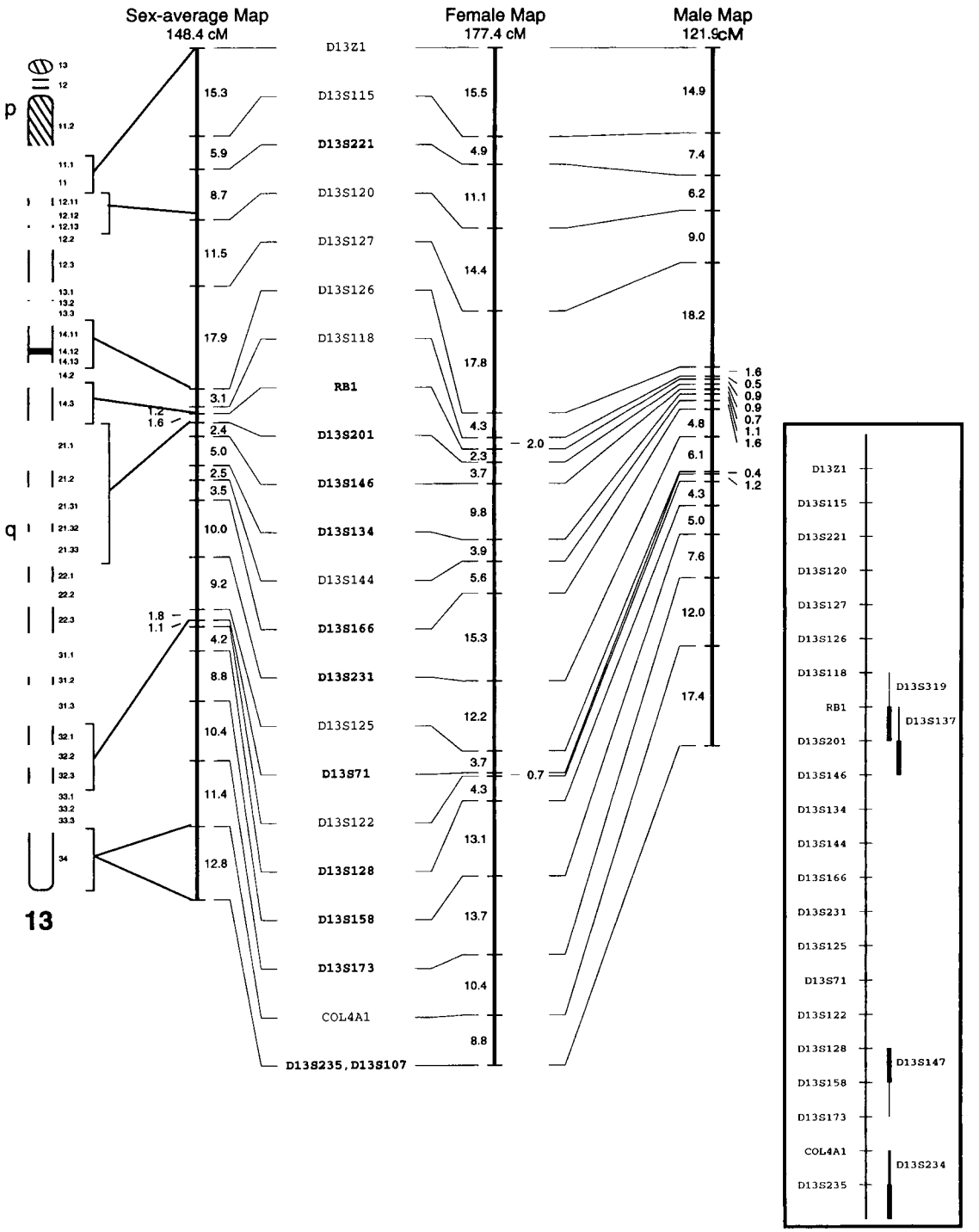

Fig. 13. The EUROGEM Map of Human Chromosome 13

J. Attwood[a]
T. Kruse[b]
G. Vergnaud[c,d]
P. Malaspina[e]
S. Povey[a]

The EUROGEM Map of Human Chromosome 14

[a] MRC Human Biochemical Genetics Unit, University College London, UK;
[b] Institute of Human Genetics, University of Aarhus, Denmark;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Centre d'Études du Bouchet, Vert le Petit, France;
[e] Dipart. di Biologia, II Universita di Roma "Tor Vergata", Roma, Italy

A framework map was constructed using corrected data from the CEPH Consortium [37]. The MultiMap program [8] was used to construct a well-supported framework of markers spaced at 10-20cM intervals from this dataset. This map was then used as a starting point for CRI-MAP 'build', 'flips' and 'chrompic' runs to incorporate the EUROGEM data.

After removal of intralocus recombinants, the EUROGEM markers were submitted to CRI-MAP in decreasing order of informativeness to be built into the framework map. Géenéthon markers were made into haplotyped systems (hap_sys0) with their CEPH counterparts but, otherwise, EUROGEM markers replaced duplicate systems in the framework map. After each 'build' run, the result was tested with 'flips2' and markers not supported were removed. When no more markers could be added, the remaining markers were temporarily inserted in their most likely positions and 'chrompic' output generated. This was examined for double recombinants in short distances and single recombinants clustered in families. Suspicious data were rechecked by the contributing laboratory and the map rebuilt. The final order was found to be supported at odds of at least 1000:1 by four-way 'flips'.

13 markers have been typed by the EUROGEM collaboration and 9 of these including 6 Généthon markers have been fitted uniquely into the map, which has a length of 146.2 cM (sex-averaged) and extends from ANG to D14S20.

The total length of the CEPH Consortium map of chromosome 14 [37] is 163cM (sex-averaged), but this includes an additional locus IGH at a distance of 12 cM beyond D14S20/S23, the most distal markers on the map presented here, so that for the comparable regions the two maps are similar in length. The CHLC map [4] is also comparable in length (153 cM). The order of D14S20 and D14S23, the most likely distally placed markers on the current map, estimated to be 3.2 cM apart (sex-averaged), agrees with that given in [4] but is reversed from that in the CEPH Consortium map [37]. The immunoglobulin heavy chain locus, IGH, could not be positioned with certainty in our map but its most likely position is distal to D14S20/S23 as shown in the CEPH Consortium map.

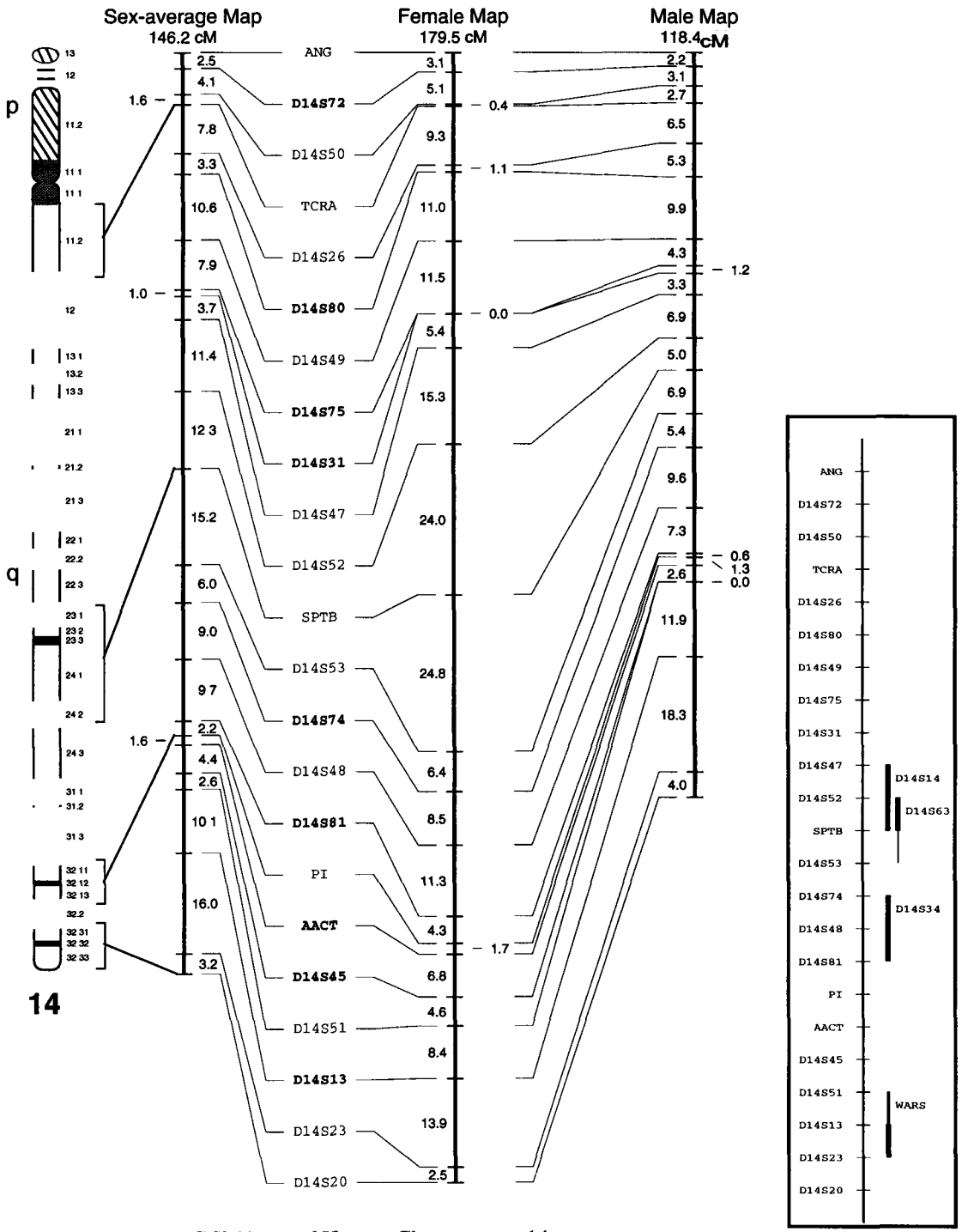

Fig. 14. The EUROGEM Map of Human Chromosome 14

C. Joyce[a]
L. Fanning[a]
S. Malcolm[b]
I. Richard[c]
O. Broux[c]
J.S. Beckmann[c]
T. Flint[d]
T.A. Kruse[d]
G. Vergnaud[e,f]
S.A. Cox[h]
O. Sandro[g]
L. Contu[g]
T.V. McCarthy[a]

The EUROGEM Map of Human Chromosome 15

[a] Department of Biochemistry, University College Cork, Ireland;
[b] Institute of Child Health, University of London, UK;
[c] CEPH/Généthon Paris, France;
[d] University of Aarhus, Institute of Human Genetics, Aarhus, Denmark;
[e] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[f] Centre d'Études du Bouchet, Vert le Petit, France;
[g] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy
[h] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), South Mimms, Hertfordshire, UK;

Human chromosome 15 is an acrocentric chromosome which accounts for approximately 3.3% of the relative autosome length. The mean genetic length of this chromosome in males, taken from an analysis of chiasma counts, is 100 cM [32]. The long arm is estimated to be 89 Mb and the short arm, 17 Mb.

A number of important human diseases have been localised to human chromosome 15 by genetic linkage analysis including Marfan syndrome, Ectopia Lentis and the recessive form of limb-girdle muscular dystrophy. In the last three years, a number of partial and full linkage maps of chromosome 15 have been constructed, including the NIH/CEPH, CEPH and Généthon maps [38,39,2,7,15,3]. 29 loci were placed on the CEPH maps respectively with likelihood support of at least 1000:1. Multipoint linkage analysis in the CEPH map provided estimates that the male, female and sex-averaged maps extend for 127, 190 and 158 cM respectively. The largest interval was 21 cM and the average locus spacing was 5.6 cM. 27 loci were placed on the Généthon map with an estimated genetic length of 107 cM. The largest gap was 12 cM and the average locus spacing was 4 cM. More recently, Beckmann and colleagues [15] have placed 58 loci on the map with likelihood support of at least 1000:1. The male, female and sex-averaged maps extend for 106, 150 and 128 cM respectively. The largest genetic interval was 11 cM and the average locus spacing was 2 cM.

In this work, 33 polymorphic genetic markers were placed on the map with odds for order of at least 1000:1. Genotypings for fifteen microsatellite based markers (D15S118, D15S120, D15S10, D15S143, D15S146, D15S119, D15S123, D15S126, D15S161, D15S132, D15 S221, D15S172, THBS, D15S129 and FBN1) and 7 RFLP-based markers (ANPEP, D15S105, Gem-152, FMN, D15S13, D15S24 and D15S10) were generated as part of the EUROGEM initiative using the CEPH reference pedigrees. Ten of the loci have been haplotyped.

The male map is 132.6 cM in length, the female map is 216.1 cM and the sex-averaged map is 169.9 cM. Thus, this map compares well with previously reported maps. The largest intervals on the sex-equal map are 15.2 cM. On the male genetic map, 9 intervals exceed 5 cM and on the female genetic map, 16 intervals exceed 5cM. The average locus spacing is 5.1 cM.

17 microsatellite markers on this map are included in both the Généthon linkage map [3] and on the map constructed by Beckmann and colleagues [15] and the order has remained unchanged. The map also contains 11 of the reference markers from the "First International Workshop on Human Chromosome 15 Mapping" [40]. One of the markers (D15S129) has been physically mapped by in situ-hybridisation to 15q15.1 [41]. Markers which were genotyped previously in the eight large CEPH families were retyped in the 40 reference pedigrees and checked for intralocus recombinants. One marker, D15S26, typed in the 40 CEPH reference pedigrees, was submitted by two different laboratories and no errors were detected in the duplicate typings. 10 of the markers, namely D15S118, D15S221, D15S146, D15S129, D15S132, D15S123, D15S126, D15S105, Gem-152 and FMN showed heterozygosity of greater than 70%. Markers which could not be placed on the map with likelihood support of greater than 1000:1 have their most likely positions shown on the inset figure.

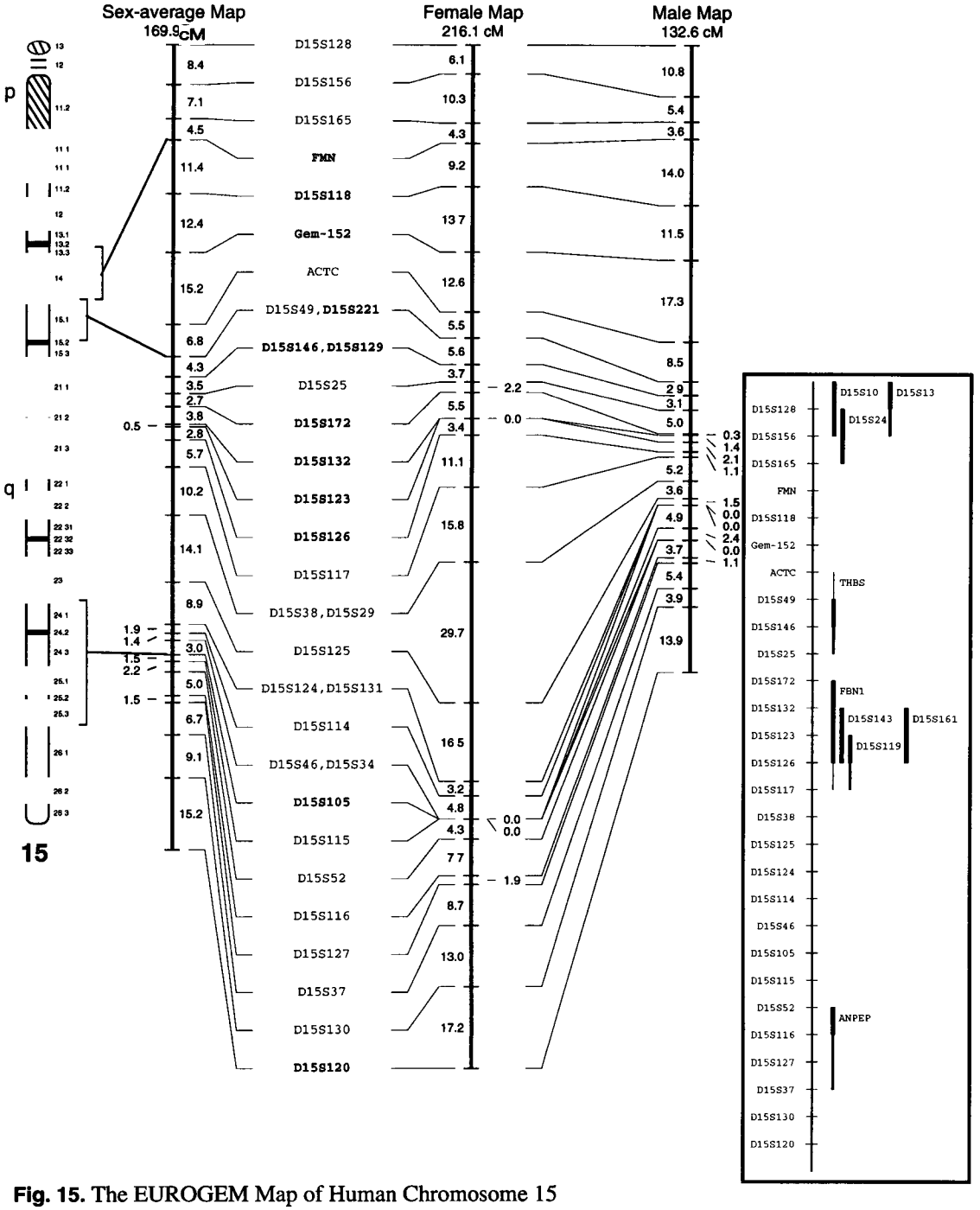

Fig. 15. The EUROGEM Map of Human Chromosome 15

S.A. Cox[a]
S. de Almeida[b]
H. Rosa[b]
G. Vergnaud[c,d]
T. Kruse[e]
J. Lavinha[b]

The EUROGEM Map of Human Chromosome 16

[a] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), South Mimms, Hertfordshire, UK;
[b] Human Genetics Laboratory, Instituto Nacional de Saúde Dr. Ricardo Jorge, 1699 Lisboa Codex, Portugal;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[d] Centre d'Études du Bouchet, Vert le Petit, France;
[e] Institute of Human Genetics, University of Aarhus, Denmark

There were 13 markers detecting 12 loci on chromosome 16, genotyped as part of the EUROGEM first phase. Four markers were Généthon (CA)n repeat markers. Three VNTR markers 3'HVR/MspI (D16S85), pEKMDA2.1/TaqI (D16S83) and p79-2-23/TaqI (D16S7) typed by the Portuguese (S de A, HR and JL) unveiled several null and complex alleles that made it very difficult to interpret the genotyping data.

The framework map that was constructed is based on the CHLC version 2 map [4]. The CHLC map was selected because of the number of chromosome 16 reference markers [42]. There are also a number of new PCR markers in the CHLC map. GV typed two different systems (CEB50/HaeIII and MS637/HaeIII-HinfI) that detect the locus D16S307. The genotype data for these two markers were haplotyped together.

The 'all' option of CRI-MAP [5] was used to place the EUROGEM markers in the CHLC map. The 'chrompic' option was run on the resulting order and a number of intralocus recombinants were detected. The intralocus recombinants were in the loci D16S85, D16S83 and D16S7. All the intralocus recombinants were physically removed, except those involving D16S83 where there were too many recombinants. The EUROGEM marker for D16S83, was left out of any further analysis.

The marker DPEP1 was also not considered further because the data lacked information and it was possible to place it at either end of the chromosome.

The revised map had a local support of 1000:1 when checked with 'flips2.' However, when the order was checked with 'flips4' there were two orders that were within the 1000:1 odds at the telomeric end of the p arm. To resolve this, the CHLC marker for D16S83 had to be added to the map.

The map contains 39 loci, 10 of which were typed within EUROGEM. These EUROGEM maps are about 30 cM longer than the CHLC maps. We do not feel that this can be explained by the extra length contributed by the 5 EUROGEM loci at the p telomere, 2 of which are present in the CHLC map. There is a large gap of 46.5 cM in the female CHLC map. It has been possible to place a marker in this gap in the EUROGEM map.

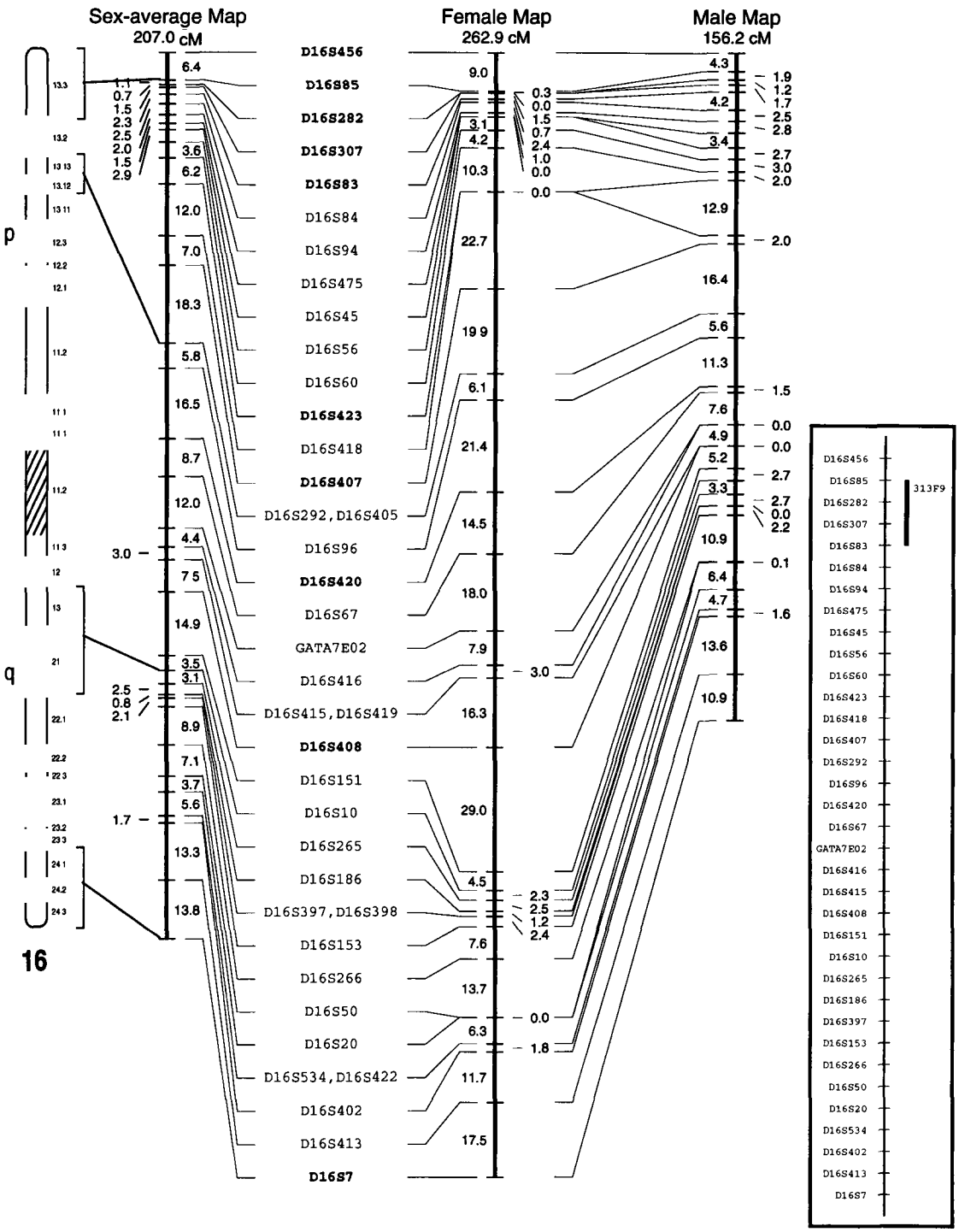

Fig. 16. The EUROGEM Map of Human Chromosome 16

S. A. Cox[a]
G. Vergnaud[b,c]
J. Milan[d]
F. Moreno[d]
J. Beckmann[e]
T. Kruse[f]
L. Contu[g]

The EUROGEM Map of Human Chromosome 17

[a] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), South Mimms, Hertfordshire UK;
[b] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[c] Centre d'Études du Bouchet, Vert le Petit, France;
[d] Unidad de Genética Molecular, Hospital Ramón y Cajal, 28034 Madrid, Spain;
[e] CEPH Paris, France;
[f] Institute of Human Genetics, University of Aarhus, Denmark;
[g] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy

During the first phase of the EUROGEM genetic mapping project 19 polymorphic marker systems detecting 18 loci on chromosome 17 were typed. Nine of the markers typed were (CA)n repeat markers, of which 7 were Généthon markers.

The genotype data was submitted to the anonymous ftp server ftp.gene.ucl.ac.uk in CEPH text format. LINK2SUM was used to check the data for allelic exclusions. Five markers were found to contain allelic exclusions and the originators were asked to check their data. After this preliminary round of error checking was done and the corrections received, a map containing only EUROGEM markers was constructed using the 'build' option of CRI-MAP [5].

In the CEPH version 6 chromosome 17 database there are 44 markers coding for 20 of the 24 chromosome 17 reference markers [43]. Duplicate typings of the same system and/or typings of different marker systems coding for the same loci were haplotyped together. The genotype data from these markers were combined with the EUROGEM genotype data and a second map constructed using the 'build' option of CRI-MAP. The tolerance for exclusion of loci was 1000:1 for this build run. Any EUROGEM or reference markers that were not included in the map during the 'build' were fitted into the map by use of the 'all' option of CRI-MAP. At this stage the 'chrompic' option of CRI-MAP was used to find intralocus recombinants. Where possible, the data in intralocus recombinants were checked. If there were still intralocus recombinants after the genotype data had been checked or if the genotype data could not be checked, all the data relating to the recombinant were removed. After the removal of all intralocus recombinants 'flips2' was run on the map and after each subsequent run, a marker was removed until the local support for the map order was 1000:1 or greater. If there was choice of either removing a EUROGEM locus or a reference locus the reference locus was removed. The resulting map contained 29 loci made up of 15 EUROGEM loci, 2 of which are chromosome 17 reference loci, and 14 other reference loci.

The 'chrompic' option of CRI-MAP was run on this 1000:1 map to detect possible data errors. Where possible data errors were found, contributors were contacted and asked to check their data. The 'all' option of CRI-MAP was used to add Généthon markers that were in the CEPH version 6 chromosome 17 database and were not also EUROGEM loci to the map. 'flips2' was run on the this map and markers were removed in a stepwise fashion until the local support was 1000:1 or greater for the placement of the markers. The 'chrompic' option was run again and data errors removed. After the removal of all remaining probable data errors from the dataset,'flips4' was run to check the order of markers was supported by odds of 1000:1.

The framework map contains 16 of the 18 EUROGEM loci, one other (D17S889), regionally located, while Gem-321 could not be placed because the most likely positions for this marker are at either the p-ter or q-ter ends of the chromosome. The map contains 17 other loci, of which 4 are Généthon markers and 13 are reference markers for chromosome 17. The female and male map are 185.5 cM and 131.7 cM respectively which is slightly shorter than the recent CHLC framework map [4]. In the sex-averaged map there are four distances between markers of more than 10 cM. The extensive error checking performed during the construction of this map may be the reason why it is shorter than the CHLC map.

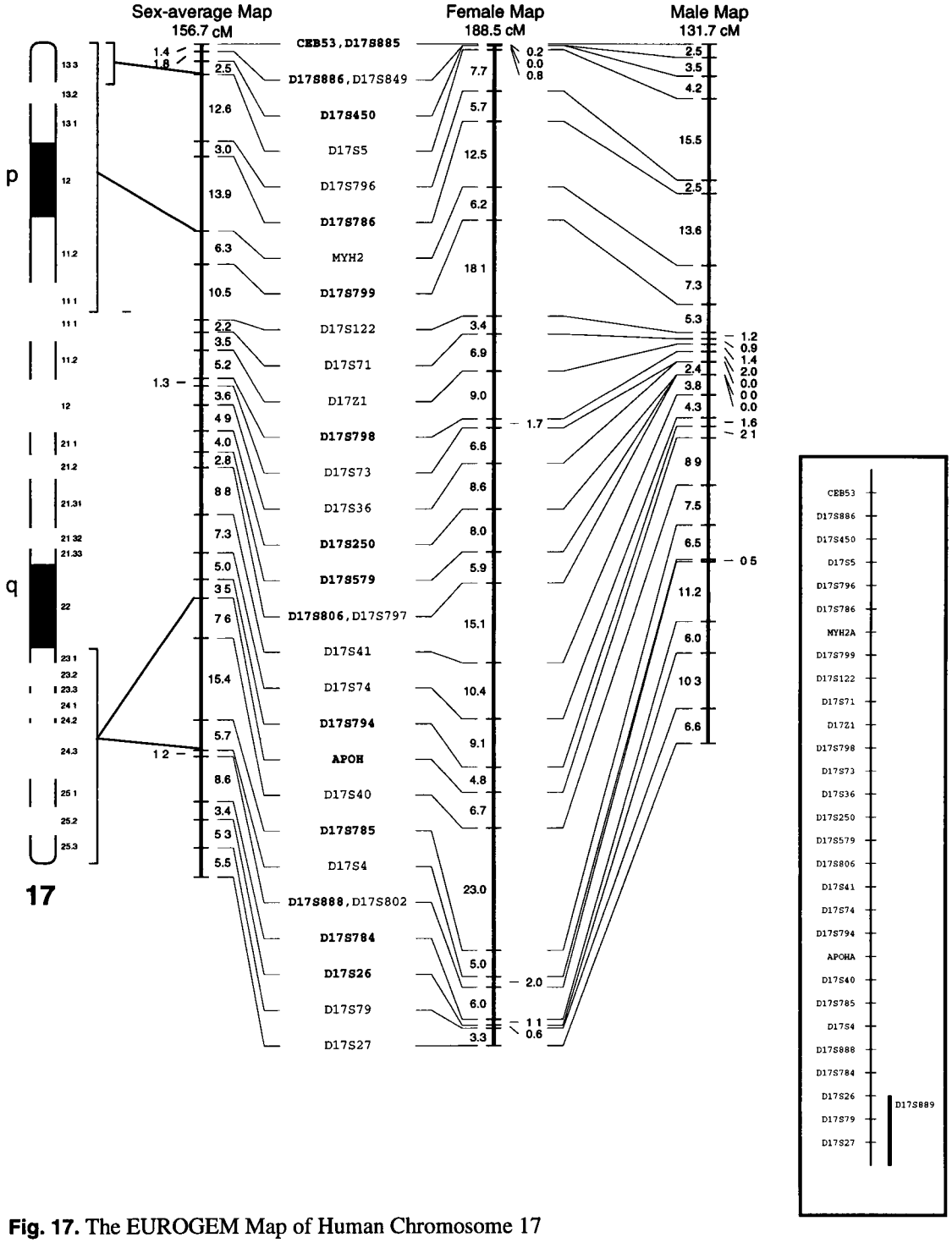

Fig. 17. The EUROGEM Map of Human Chromosome 17

M.A. Aldred
K. Wakefield
H. J. Evans
A.F. Wright

The EUROGEM Map Of Human Chromosome 18

MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK

At the commencement of this study, chromosome 18 was relatively poorly mapped. The initial maps published by Donis-Keller et al. [44] and O'Connell et al. [45] consisted of nine and twelve RFLP markers respectively and contained large gaps. In 1992, Weissenbach et al. [2] published a map containing 21 microsatellite markers, and while this represented a significant improvement over previous maps, the markers were not ordered relative to RFLP markers contained in those earlier maps.

As part of the EUROGEM project, we have extended the genotyping of 13 of the markers isolated by [2] and have also typed two other microsatellite markers [46]. These data were combined with all available chromosome 18 data from the CEPH database (version 6), in order to construct an integrated map of the chromosome. We have constructed a framework map of 21 loci that combines at least one marker from each of the previously published maps [44,45,2,46]. The total length of the sex-averaged map is 162.9 cM, with an average distance of 8 cM between markers and largest gap being 14.3 cM.

All chromosome 18 data present in version 6 of the CEPH database (a total of 53 loci) were extracted and merged with new data generated in this laboratory for the following markers: D18S37, D18S44, D18S52, D18S53, D18S56, D18S57, D18S58, D18S59, D18S60, D18S61, D18S62, D18S65, D18S66, D18S67 and D18S70. Markers that had greater than 30 informative phase-known meioses (n=53) were included in the generation of a preliminary linkage map. All analyses were carried out using the CRI-MAP program version 2.4. Local support for the preliminary map was assessed using 'flips2'. The data were then evaluated for double recombination events using the 'chrompic' option of CRI-MAP. Double recombinants in an interval of less than 20 cM were considered to be erroneous. These data were checked and corrected where possible, or excluded from further analyses otherwise. The revised data were used to construct three independent maps, one starting from pter, one from qter, and a third that incorporated the loci in decreasing order of informativeness. A composite map was then obtained.

The resulting framework map shown in the figure consists of 21 loci, of which 15 are microsatellite markers and six are RFLP markers that provide points of reference between this and earlier maps. The only EUROGEM marker that could not be integrated was D18S66. Analysis with 'flips5' showed that the minimum level of support for this order of markers is 10,000:1 for sex-specific analysis and 1000:1 for sex-averaged data. No inconsistencies were detected in the order of loci between the current and previously published genetic and physical maps [44,45,2,46,47,8,4].

On the sex-averaged map, the mean distance between markers is 8 cM and the largest gap is 14.3 cM, comparing favourably with three recently published maps [46,4,8]. The overall length of the map (162.9 cM sex-averaged) is greater than that in other reports [45,46,4,8]. This is mainly due to the inclusion of more distal markers on the short arm of the chromosome, where this map extends approximately 40 cM distal to D18S21. This and the integration of Généthon data with existing reference markers makes it a useful complement to other recently published maps of chromosome 18.

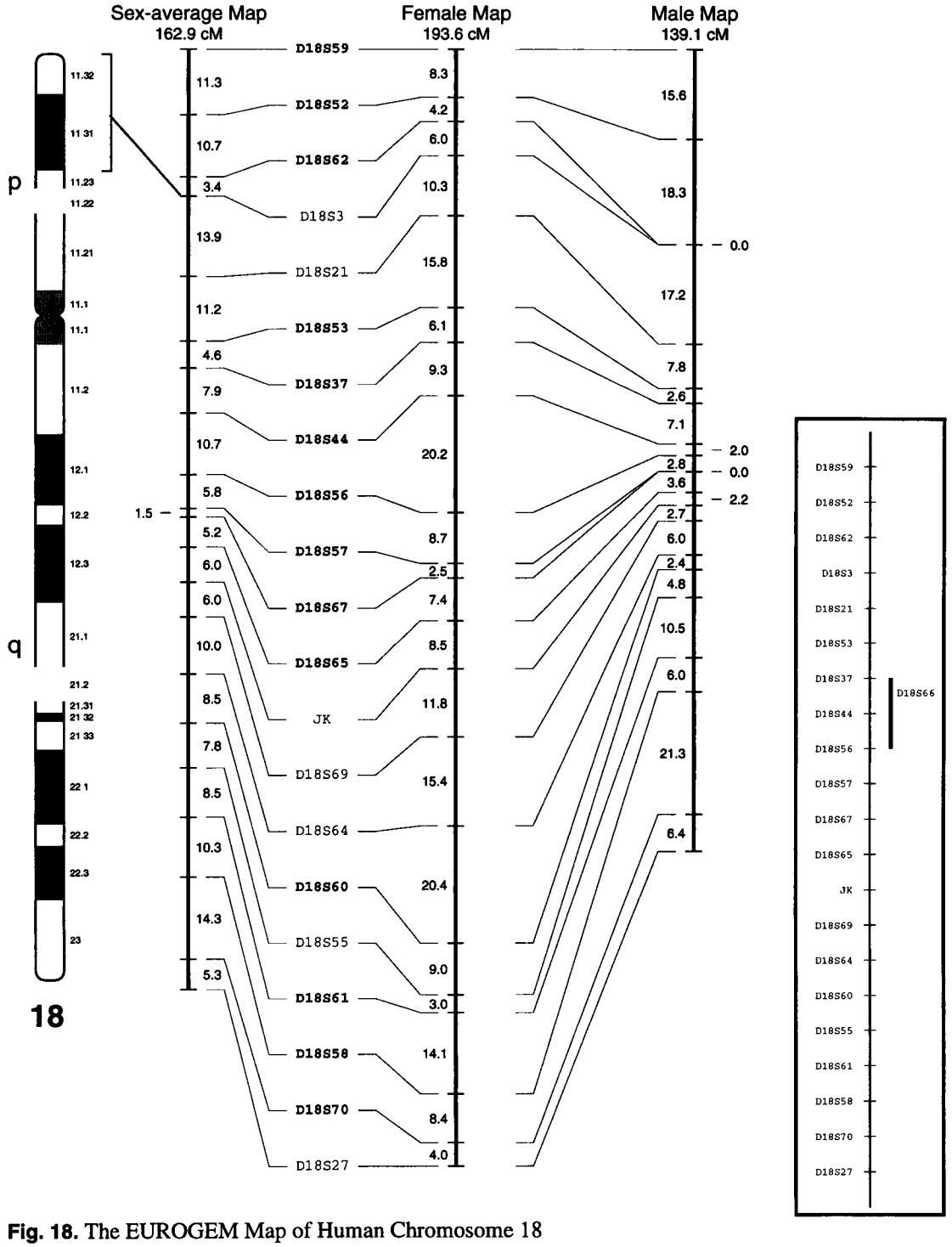

Fig. 18. The EUROGEM Map of Human Chromosome 18

S.A. Cox[a]
H. Harley[b]
R.A. Akhtar[b]
T. Kruse[c]
G. Vergnaud[d,e]

The EUROGEM Map of Human Chromosome 19

[a] Human Genetic Resources Unit (HGR), Imperial Cancer Research Fund (ICRF), South Mimms, Hertfordshire, UK;
[b] University of Wales College of Medicine, Insitute of Medical Genetics, Cardiff, UK;
[c] Institute of Human Genetics, University of Aarhus, Denmark;
[d] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[e] Centre d'Études du Bouchet, Vert le Petit, France

For the first phase of the EUROGEM genetic mapping project, 14 polymorphic markers were genotyped on chromosme 19. Several allelic exclusions were detected in the submitted data. Contributors were asked to check their data. Five of the markers (pBB2.7/EcoRI, pBB2.7/PvuII, DM-CTG/PCR, HH71/72/HinfI and HH71/89/BpmI) detected the myotonic dystrophy locus.

The CHLC version 2 map [4] was used as a framework map to which the EUROGEM loci were added. The 'all' option of CRI-MAP [5] was used to place the EUROGEM loci in the CHLC map. 'chrompic' was run on the resulting map to check for intralocus recombinants. A large number of intralocus recombinants were detected. The contributor was asked to recheck the data they had submitted. Not all the intralocus recombinants were resolved. The EUROGEM marker D19S190 was omitted from any further map building due to intralocus recombinants detected in 11 families. Only two of the markers for the DM locus were used, namely pBB2.7/EcoRI and pBB2.7/PvuII.

The remaining intralocus recombinants were removed and the local support for the map order was detemined by using 'flips2'. A stepwise removal of loci ws employed until the odds against an alternative order for the loci were 1000:1. 'flips4' was run on the new order and no further changes were needed.

The framework map contained 41 loci. Seven of the nine EUROGEM loci are incorporated into this map. The maps (female, male and sex-averaged) are all of a similar size, as are the CHLC maps. However, the EUROGEM maps are approximately 35 cM longer. The extra length of the maps is due entirely to the EUROGEM markers inserted into the map which, except for PLAUR, are all distal to the DM locus. Physical mapping data [48,49] supports the order BCL3 - APOC1 - APOC2 - D19S63 - D19S101 - DM - D19S62; whereas the EUROGEM map suggests the order BCL3 - APOC2 - DM - D19S62 - D19S101 - APOC1 - D19S63.

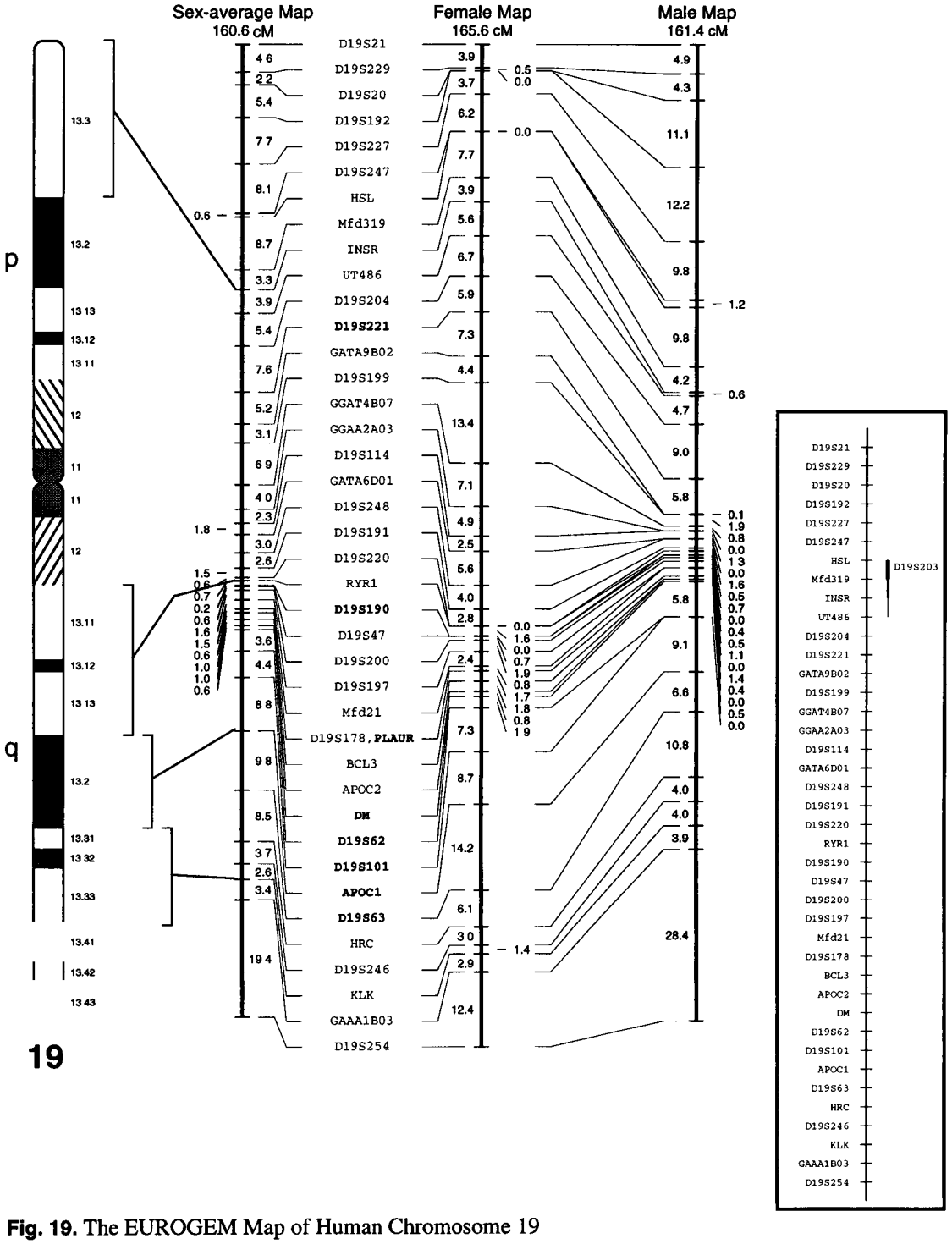

Fig. 19. The EUROGEM Map of Human Chromosome 19

V. Wunderle[a]
C. Dib[a]
C. Fizames[a]
J. Morissette[a]
J. Hazan[a]
I. Hansmann[b]
D. Whitehouse[c]
G. Vergnaud[d,e]
J. Weissenbach[a]

The EUROGEM Map of Human Chromosome 20

[a] Généthon, Evry, France and CNRS URA1445, Institut Pasteur, 75724 Paris Cedex, France;
[b] Institute für Humangenetik, D-37073 Gottingen, Germany;
[c] MRC Human Biochemical Genetics Unit, University College London, UK;
[d] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France;
[e] Centre d'Études du Bouchet, Vert le Petit, France

A number of linkage maps of chromosome 20 which have been reported to date mainly integrate existing genotyping data [7,8,4], whereas some others correspond to original data [50,2,51,3]. The present map is based on a total of 45 markers that were genotyped on a large majority of the forty CEPH families by the EUROGEM network. Four of these markers (D20S33, D20S136, D20S137 and B6.7) were minisatellite,s whereas the other 41 were microsatellites from previous linkage maps of chromosome 20 [50,3]. The heterozygosities range from 46% to 92% and 32 of the markers including all minisatellites show heterozygosities above 70%. D20S137, D20S33 and D20S136 have been mapped by fluorescent in situ hybridization respectively to 20p11.2, 20q13.1 and 20q13.3 [52,53].

Data checking and map construction using MultiMap was carried out as described in Villamar et al. (this publication).

The sex-averaged map covers a linkage distance of 139 cM. The largest comparable map segment shows a reduction of 13 cM compared with Hazan and colleagues [50] and an increase of 7 cM with Gyapay and colleagues [3], whereas integrated maps of [8] and [4] extend further on 20q. The present map extends 11 cM distally on 20p compared with Gyapay and colleagues [3] and 24 cM distally on 20q compared with Hazan and colleagues [50]. A total of 32 markers could be ordered with odds ratios above 1000:1. Surprisingly, six markers that were unambiguously ordered in [50] could not be ordered on the present map. More expectedly, 6 markers that were not unambiguously ordered in [50] could be placed in well-supported order on this map. A discrepancy between [50] and the present map was observed in the order of D20S39 and D20S52. Two markers ordered with odds ratios above 1000:1 in [3] were not unambiguously placed on this map but all other orders were identical on both maps. The discrepancies with Hazan and colleagues [50] mostly result from a few discrepant genotypes observed in some individuals. In addition some families typed in [50] were not from the original set of 40 CEPH pedigrees that was analysed here.

Although the mean interval size is close to 3 cM the map shows a total of 4 intervals above 10 cM. The largest remaining gaps are located between D20S55 and D20S33 (16.5 cM) and between D20S59 and D20S186 (14.6 cM). These areas are however much better covered in the most recent version of the Généthon map and could thus easily be filled by additional PCR based markers. The most distal intervals (11.0 and 13.2 cM) denote a persisting dearth of such markers which also appears in Gyapay and colleagues [3]. Genotyping of a few additional microsatellite markers placed in poorly covered areas in the next EUROGEM programme will readily allow us to obtain a high resolution map of human chromosome 20.

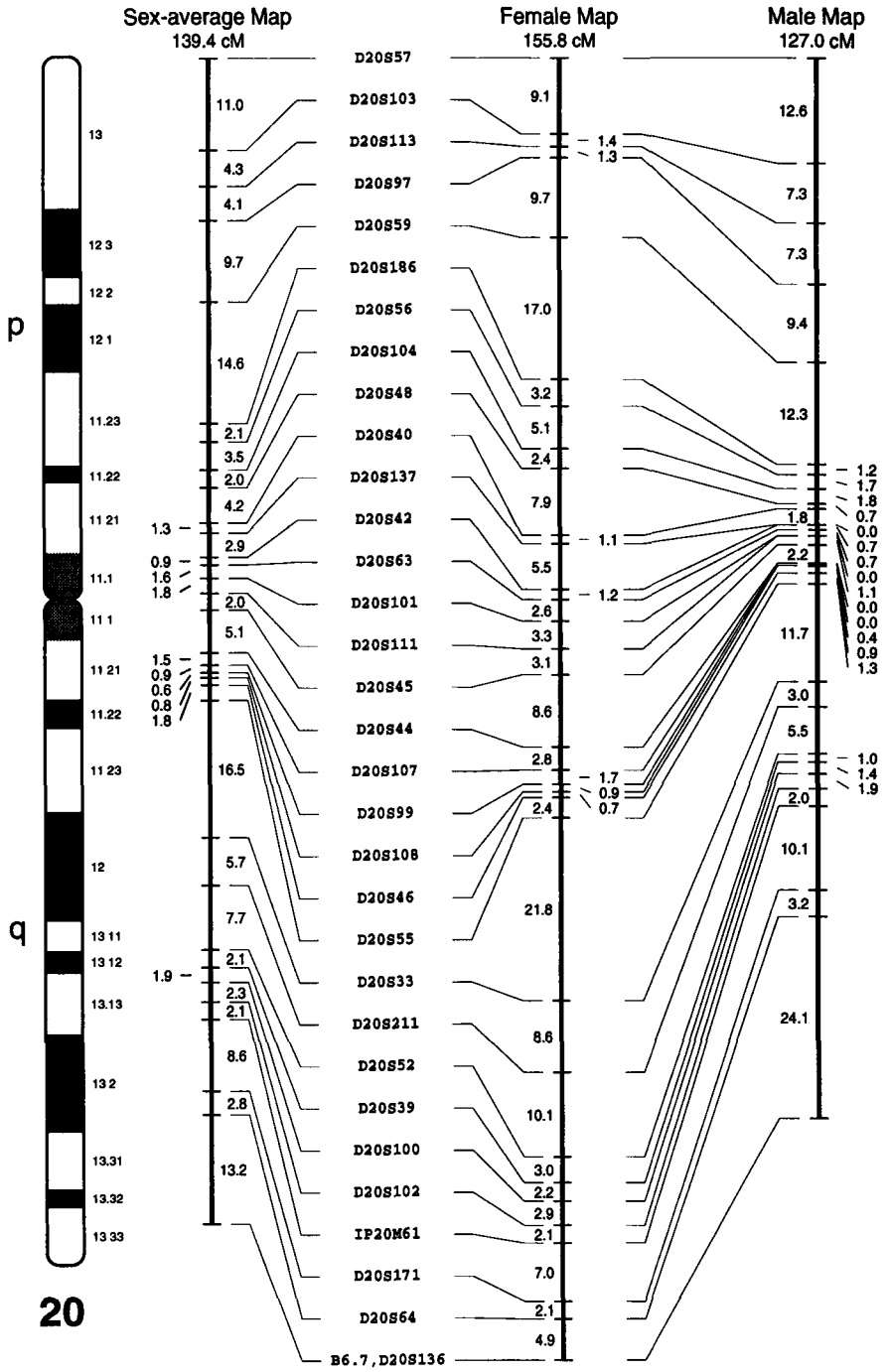

Fig. 20. The EUROGEM Map of Human Chromosome 20

A. Bosch[a]
J. Guimerà[a]
A. Pereira de Souza[b]
X. Estivill[a]

The EUROGEM Map of Human Chromosome 21

[a] Molecular Genetics Department, Cancer Research Institute, Barcelona, Catalonia, Spain;
[b] CEPH/Généthon, Paris, France

Human chromosome 21 is the smallest human autosome, representing less than 2% of the human genome. The long arm has been widely studied and its estimated length is about 40 Mb.

The chromosome 21 linkage map has been considerably improved recently using 43 markers, with an average interval of 2.5 cM [54], but still many polymorphic markers have to be developed and added to the genetic map to reach the 1 cM resolution necessary to locate polygenic disorders. Microsatellite sequences are the best markers for building linkage maps as they are highly polymorphic, easy to analyse using PCR and they are uniformly spread throughout the human genome. To improve the linkage map of chromosome 21, and under the EUROGEM Project, 22 CA-repeat markers, with an average heterozygosity of 0.71, were genotyped using the CEPH reference families and a genetic map with 44 highly polymorphic markers was constructed using multilocus linkage analysis with the CRI-MAP program. The framework map was built by first constructing 3 different maps following the same criteria outlined in the construction of the map for chromosome 12 (AB et al., this publication).

Twenty-two index markers were chosen from available genotype databases (CEPH version 6 and CHLC version 2) with an average heterozygosity of 0.79. Together, the markers used in this map have an average heterozygosity of 0.75. In total, 39 dinucleotide repeats, 3 tetranucleotides, 1 VNTR and 1 RFLP marker were used. The linkage map contains 39 uniquely placed loci ordered with odds of at least 1000:1 and any alternative order was excluded by permutations of 4 neighbouring loci. Four additional markers were positioned on the map approximately. The framework map consists of 24 anchor points, 10 of them megaloci, containing from 2 to 4 markers. The sex-average length of the map is 68.9 cM, about 3.5 cM longer than a previous published map [54], due to higher male recombination rate at the telomere (male and female lengths are 57.8 and 80.5 cM, respectively). On the sex-average map the 23 intervals have an average length of 3.0 cM, with the two largest gaps having a length of 5.4 cM (between D21S11 and D21S414, and between D21S65 and D21S167). The largest gap in the previous genetic map was 6.3 cM located above D21S11. This gap has now been filled with 4 new markers (D21S406, D21S364, D21S1266 and D21S409) at distances of 1.4, 0.3, and 0.9 cM respectively. Of the 22 markers genotyped for this project, 18 fit uniquely in the framework map. Among the other 4 markers, D21S1234 was found to be the same marker as D21S415, D21S156 inflated considerably the length of the map, so it was only positioned approximately, as were D21S1419 and D21S1421, which could not be placed uniquely on the map. This work provides 22 markers that have not previously been localised in a linkage map [55]. In the present map, the position of these markers is consistent with their cytogenetic location, and the index markers included also have equivalent relative locations to the previously reported maps [7,2]. These 22 new markers will contribute greatly to the integrated genetic map, and also to the construction of a map, based only on highly polymorphic markers, with the desired 1 cM resolution. The inclusion of these markers in the YAC map [55] provides a more refined location, allowing the integration of the linkage, cytogenetic and physical maps of chromosome 21 [56].

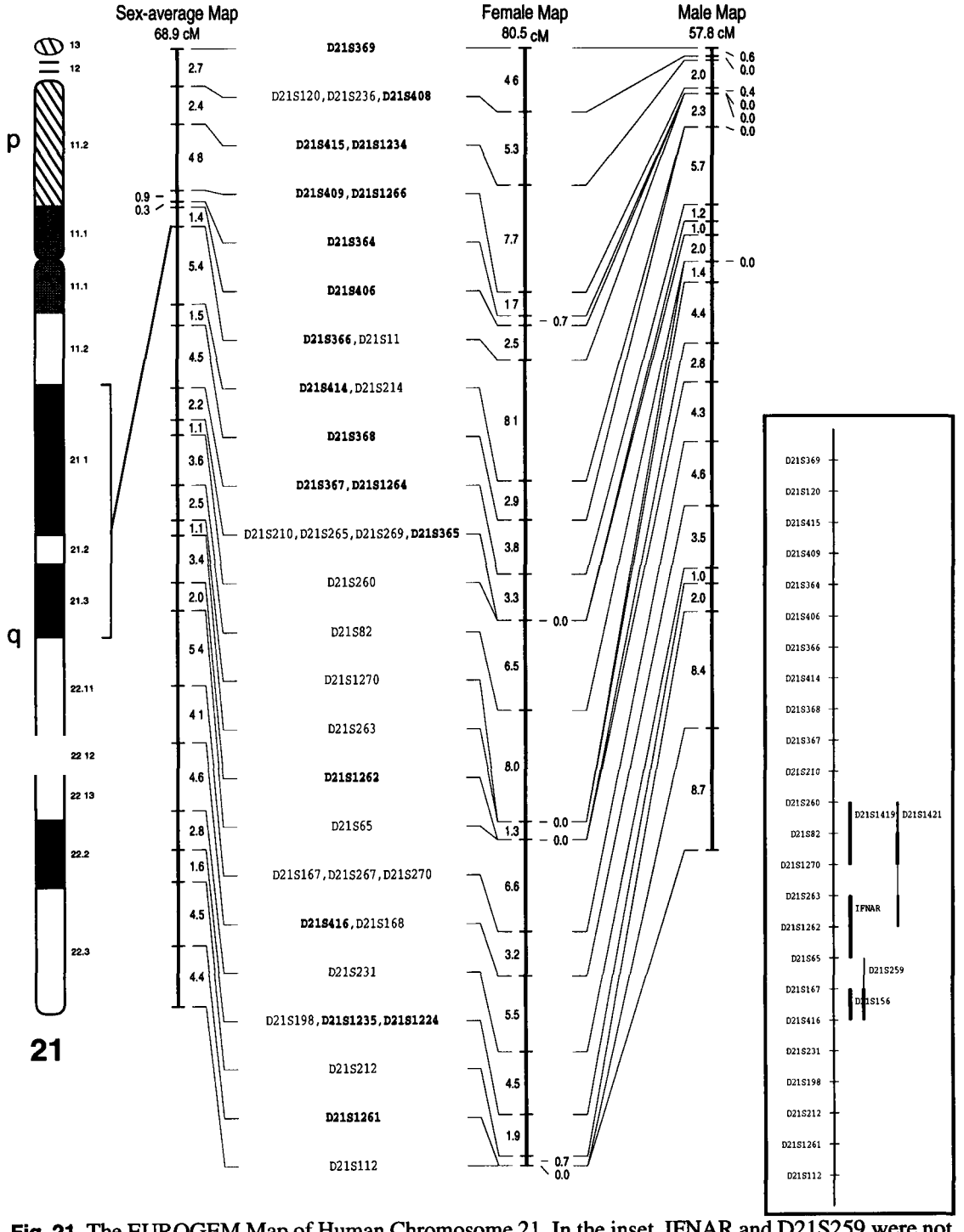

Fig. 21. The EUROGEM Map of Human Chromosome 21. In the inset, IFNAR and D21S259 were not typed within EUROGEM.

B.P. Riley[a]
R. Williamson[a]
G. Vergnaud[b,c]

The EUROGEM Map of Human Chromosome 22

[a] Department of Biochemistry, St Mary's Hospital Medical School, London, UK;
[b] Centre d'Études du Bouchet, Vert le Petit, France;
[c] Laboratoire de Génétique des Espèces, Institut de Biologie, Nantes, France

Chromosome 22 is one of the smallest human chromosomes and contains numerous ribosomal sequences and is similar to chromosome 21 in these two respects. Unlike chromosome 21, however, it is not associated with a non-lethal trisomy, and has therefore been investigated less thoroughly and for a shorter time. The characterisation of the Philadelphia chromosome, and its translocation involved in chronic myeloid leukaemia, brought about new interest in chromosome 22, and its small size has actually benefited its profile in the molecular biological research community. Most of the chromosome is now mapped in overlapping yeast artificial chromosomes (YACS), and chromosome 22 is likely to be the first to be completely mapped and sequenced. Medical genetics researchers have also had their interest renewed in chromosome 22 recently, due to the discovery of the deletion causing Velo-Cardio-Facial (VCF) syndrome and recent efforts to find regions of the q arm linked to psychotic illness. This interest continues, as the deletion region has been suggested to be a marker for non-Di George heart defects. Many genes (e.g. catechol-O-methyl transferase (COMT) and the break-point cluster region gene (BCR) have been mapped to chromosome 22 as well, demonstrating clearly that chromosome 22 is of much greater genetic and molecular interest than was once thought.

The present map consists of 18 markers unambiguously assigned positions with odds greater than 1000:1. Five new markers have been added to the existing genetic map during the first round of the EUROGEM project, D22S266, D22S267, D22S408, D22S409 and D22F101S1. Three of these five (D22S409, D22S267 and D22F101S1) could not be placed into a single interval with odds of greater than 1000:1, and have been given regional assignment. These polymorphic probes are minisatellites isolated from a chromosome 22 cosmid library constructed at the Lawrence Livermore Laboratory under the auspices of the US Department of Energy (contract number W7405-ENG-48). D22S266 (CEB31), D22S267 (CEB17), D22S409 and D22F101S1 were isolated by screening the gridded chromosome 22 cosmid library with synthetic tandem repeats (16C17 and 16C27 in the cases of D22S266 and D22S267), [52]. D22S408 was isolated using as yet unpublished procedures (GV et al., in preparation). None of these markers have as yet been mapped by other methods. One pair of loci (D22S408 and D22S266) exhibited no recombination and have been mapped as a haplotype system. The other 16 markers are drawn from the CEPH database version 6. The markers cover a sex-averaged genetic distance of 80.1 cM. Although the present map is longer than two other recently published maps [11,2], it is considerably shorter than a third recent map [7] indicating that markers used do not extend the full length of the chromosome, but coverage to the qter is as complete as present markers allow. The excess genetic distance in the NIH/CEPH map is due to the inclusion of markers nearer the centromere. Distances between anchor loci used in two of the three previous maps and the present one compare favourably. For markers used in common with the above maps, all orders are identical, and distances are similar.

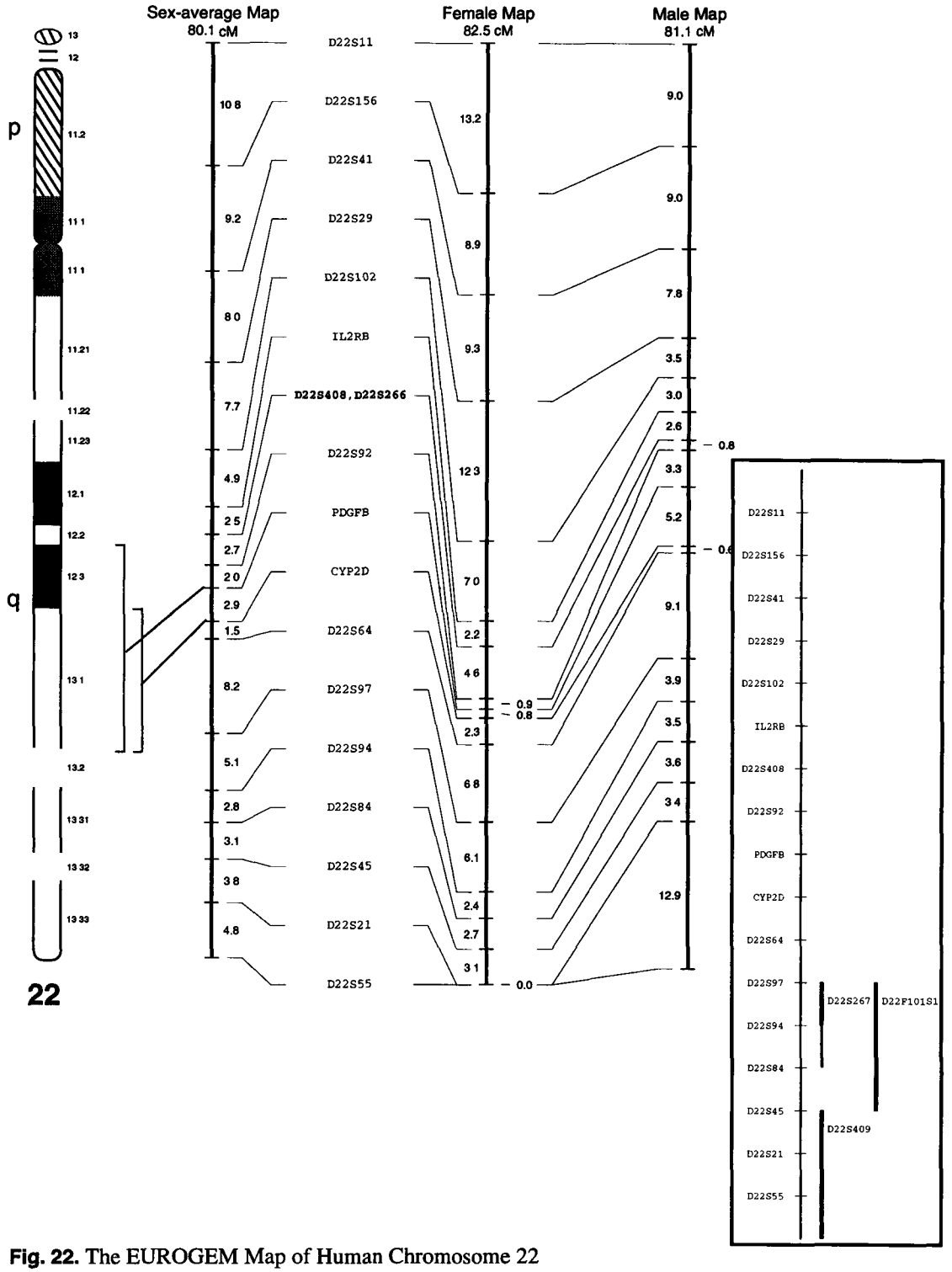

Fig. 22. The EUROGEM Map of Human Chromosome 22

M.A. Aldred[a]
T. Flint[b]
R. Vossen[c]
K. Wakefield[a]
M.A. Ferguson-Smith[d]
M. Lush[d]
D. Rubinsztein[d]
T. Kruse[b]
A. Loizedda[e]
B. Bakker[c]
J.R.W. Yates[d]
A.F. Wright[a]

The EUROGEM Map Of Human Chromosome X

[a] MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK;
[b] Institute of Human Genetics, University of Aarhus, Denmark;
[c] Department of Human Genetics, Leiden University, 2300 RA Leiden, The Netherlands;
[d] Department of Pathology, University of Cambridge, UK;
[e] Cattedra di Genetica Medica, Università degli Studi di Cagliari, Italy

The X chromosome contains a large number of polymorphic markers, but in spite of this, it has been difficult to produce high resolution maps [44,7,8,4]. Three of the most recent maps each consist of less than 25 markers and contain at least one gap of greater than 20 cM [7,8,4]. As part of the EUROGEM project, we have extended the genotyping of eleven polymorphisms in CEPH families and these data have been combined with those from the CEPH database version 6 to construct a genetic map of the X chromosome. A map 214 cM in length has been constructed that contains 33 marker loci. The average distance between markers is 7 cM and largest gap is 13.8 cM.

Markers genotyped as part of the EUROGEM project are as follows: 3 polymorphisms at PDHA (these were haplotyped together for the linkage analysis), MAOA, DXS84, DXS438, DXS984, DXS990, DXS996, DXS999 and DXS1001. These data were merged with data for all X-chromosome markers with greater that 200 informative phase-known meioses taken from version 6 of the CEPH database. Linkage analysis was carried out using the CRI-MAP program version 2.4. Reference markers from the CEPH database were chosen at 10-20 cM intervals to form a starting framework map that allows comparison with previously published maps. These loci were DXS143, DXS207, DXS274, DXS992, DXS164, DXS7, DXS255, DXYS1X, DXS425, HPRT, FRAXA and DXS15. EUROGEM markers were integrated into this reference map, followed by Généthon markers and then finally other markers from the CEPH database. At each stage, local support was checked with 'flips2', poorly supported loci (odds of <1000:1) were removed and then support for the revised map was assessed with 'flips5'.

The map constructed is shown in the figure. It contains 33 marker loci, with the average distance between markers being 7 cM and largest gap 13.8 cM. The total length is 214.2 cM. Analysis with 'flips5' shows this map to be at least 1000:1 more likely than alternative orders. Markers analysed by EUROGEM laboratories that could not be integrated into the map are DXS84, DXS438, MAOA and DXS996. The most likely positions of these markers are shown against the framework map in the figure. No inconsistencies were detected in the order of loci in this map as compared to previously published genetic maps [44,7,8,4]. The average distance between markers is similar to that in the maps of [8] and [4]. However, this map represents an improvement over those maps with regard to the total number of markers integrated (33 against 21-24) and the reduction of the largest gap from 22-25 cM to 14 cM.

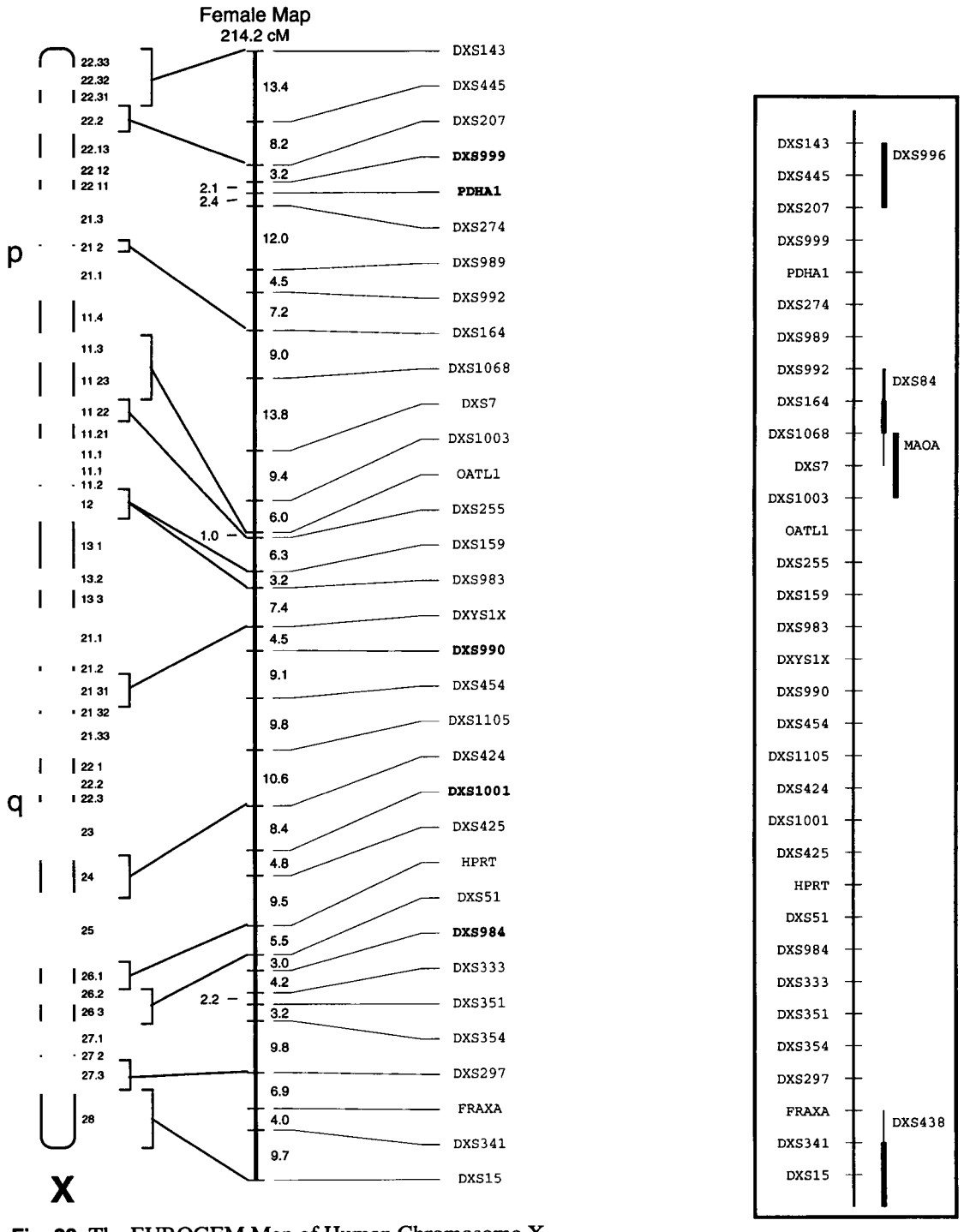

Fig. 23. The EUROGEM Map of Human Chromosome X

References

1 Dausset J, Cann H, Cohen D, Lathrop M, Lalouel J-M, White, R: Centre d'etude du polymorphisme humaine (CEPH): Collaborative Genetic Mapping of the Human Genome. Genomics 1990;6:575-577.

2 Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, Lathrop M: A second-generation linkage map of the human genome. Nature 1992;359:794-801.

3 Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, Bernardi B, Lathrop M, Weissenbach J: The 1993-94 Genethon human genetic linkage map. Nature Genetics 1994;7:246-339.

4 Buetow KH, Weber JL, Lundwigsen S, Scherpbier-Heddema T, Duyk GM, Sheffield VC, Wang Z, Murray JC: Integrated human genome-wide maps constructed using the CEPH reference panel. Nature Genetics 1994;6:391-393.

5 Green P, Falls K, Crooks S: Documentation for CRI-MAP, version 2.4; 1989:available from P. Green.

6 Spurr NK, Cox S, Bryant SP, Attwood J, Robson EB, Shields DC, Steinbrueck T, Jenkins T, Murray JC, Kidd KK et al: The CEPH consortium linkage map of human chromosome 2. Genomics 1992;14:1055-1063.

7 NIH/CEPH collaborative mapping group: A comprehensive genetic linkage map of the human genome. Science 1992;258:67-68.

8 Matise TC, Perlin M, Chakravarti A: Automated construction of genetic linkage maps using an expert system (MULTIMAP): a human genome linkage map. Nature Genetics 1994;6:384-390

9 Tory K, Schmidt L, Li H, Wie MH, Geil L, Hustad T, Latif F, Lerman M, Zbar B: Linkage map of 175 loci on human chromosome 3. Cytogenet Cell Genet 1994;65: 67.

10 O'Connell P, Rains D, Wilkie P, Garcia D, Matsunami N, Albertsen H, Weber J, Weissenbach J, White R, Naylor S: A microsatellite geneti cmap for chromosome 3. Cytogenet Cell Genet 1994;65:43.

11 Collaborative Human Linkage Center, CHLC Report 1(1), 1993.

12 Naylor SL, Buys CHCM, Carritt B: Report of the 4th international workshop on human chromosome 3 mapping. Cytogenet Cell Genet 1994;65:2-33.

13 Vignal A, Gyapay G, Hazan J, Nguyen S, Dupraz Ch, Cheron N, Becuwe N, Tranchant M, Weissenbach J: Nonradioactive multiplex for genotyping of microsatelite markers. Methods in Molecular Genetics 1993;1:211-221.

14 Banchs I, Bosch A, Guimera J, Lazaro C, Puig A, Estivill X: New Alleles at microsatellite loci in CEPH families mainly arise from somatic mutations in the lymphoblastoid cell lines. Human Mutation 1994;3:365-372.

15 Beckmann JS, Richard I, Hillare D, Broux O, Antignac C, Bois E, Cann H, Cottingham RW, Feingold N, Kalil J, Lathrop GM, Marcadet A, Masset M, Mignard C, Passos-Bueno MR, Pellerain N, Dausset J, Fardeau M, Cohen D: A gene for limb-girdle muscular dystrophy maps to chromosome 15 by linkage. C.R. Acad Sci Paris 1991;312:141-148.

16 Voltz A, Boyle JM, Cann HM, Cottingham RW, Orr HT, Ziegler, A. Report of the Second International Workshop on Human Chromosome 6. Genomics 1994;21:464-472.

17 Helms C, Mishra SK, Burgess AK, Cline SL, Knobloch D, Hing AV, Vergnaud G, Donis-Keller H: A comprehensive genetic linkage map of the human genome. Science 1992; 258:67-68.

18 Hill AS, Pratt WS, Attwood J, Robson EB, Swallow DM: Polymorphism of a MUC3 gene and its localisation within a preliminary framework map of chromosome 7. Cytogenet. Cell Genet. 1994;65:68.

19 Gurreri F, Trask BJ, van den Engh G, Krauss CM, Schinzel A, Pettenati MJ, Shindler D, Dietz-Band J, Vergnaud G, Scherer SW, Tsui LC and Meunke M: Physical mapping of the holoproscencephaly critical region on chromosome 7q36. Nature Genetics 1993;3:247-251.

20 Attwood J , Chiano M, Collins A, Donis-Keller H, Dracopoli N, Fountain J, Falk C, Goudie D, Gusella J, Haines J, Armour JAL, Jeffreys AJ, Kwiatkowski D, Lathrop M, Matise T, Northrup H, Pericak-Vance MA, Phillips J, Retief A, Robson E, Shields D, Slaugenhaupt S, Verganud G, Weber J, Weissenbach J, White R, Yates J, Povey S: The CEPH Consortium Map of Chromosome 9. Genomics 1994;19:203-214.

21 Povey S, Haines J: Report on the constitution of human chromosome 9. HGM 93. 1993; In press.

22 Povey S, Smith M, Haines J, Kwiatkowski D, Fountain J, Bale A, Abbott C, Jackson I, Lawrie M, Hulten M: Report on the first international workshop on human chromosome 9. Ann Hum Genet 1992;56:167-221.

23 Kwiatkowski DJ, Dib C, Slaugenhaupt SA, Povey S, Gusella JF, Haines JL: An index marker map of chromosome 9 provides strong evidence for positive interference. Am J Hum Genet 1993;53:1279-1288.

24 Povey S, Armour J, Farndon P, Haines JL, Knowles M, Olapade F, Pilz A, White JA, Members of the Utah Genome Centre Genetic Marker and Mapping Groups, Kwiatkowski DJ: Report on the 3rd Human Chromosome 9 Workshop. Annals of Hum. Genet. 1994;58:177-200.

25 Mao I, Simpson NE: Report of the committee on the genetic constitution of chromosome 10; in Cuticchia AJ, Pearson PL (eds): Human Gene Mapping 1993. Johns Hopkins U. Press, 1993, pp.387-406.
26 Arps S, Rodewald A, Schmalenberger B, Carl P, Bressel M, Kastendieck H: Cytogenetic survey of 32 cancers of the prostate. Cancer Genet Cytogenet 1993;66:93-99.
27 Fults D, Pedone C: Deletion mapping of the long arm of chromosome 10 in glioblastoma multiforme. Genes Chrom Cancer 1993;7:173-177.
28 Deloukas P, Dauwerse JG, Moschonas NK, van Ommen GJ, van Loon AP: Three human glutamate dehydrogenase genes (GLUD1, GLUDP2 and GLUDP3) genes are located on chromosome 10q, but are not closely physically linked. Genomics 1993;17:676-681.
29 Tzimagiorgis G, Leversha MA, Chroniary K, Goulielmos G, Sargent CA, Ferguson-Smith M, Moschonas NK: Structure and expression analysis of a novel member of the human glutamate dehydrogenase (GLUD) gene family mapped to chromosome 10p11.2 Hum Genet 1993;91:433-438.
30 Hunt D et al.: Physical mapping of 38 highly informative genetic markers to 10 intervals of chromosome 11q: integration of the physical and genetic maps. Ann. Hum. Genet. 1994;58:81-85.
31 Craig I, Gemmill R, Kucherlapati R: Report of the first international workshop on human chromosome 12 mapping. Cyt.Cell Genet. 1992;61:243-251.
32 Morton, NE: Parameters of the human genome. Proc Natl Acad Sci, USA 1991;88:7474-7476.
33 Bowcock AM, Gerken SC, Barnes RI, Shiang R, Wang Jabs E, Warren AC, Antonarakis S, Retief AE, Vergnaud G, Leppert M, Lalouel J-M, White RL, Cavalli-Sforza LL: The CEPH consortium linkage map of human chromosome 13: Genomics 1993;16:486-496.
34 Bowcock A, Osborne-Lawrence S, Barnes R, Chakravarti A, Washington S, Dunn C: Microsatellite polymorphism linkage map of human chromosome 13q. Genomics 1993;15:376-386.
35 Petrukhin KE, Speer MC, Cayanis E, Bonaldo M de F, Tantravahi U, Soares MB, Fischer SG, Warburton D, Gilliam TC, Ott J: A microsatellite genetic linkage map of human chromosome 13. Genomics 1993;15:76-85.
36 Kooy RF, Verlind E, Shapiro DN, Cowell JK, Scheffer H and Buys CHCM: A deletion hybrid breakpoint map of the chromosomal region 13q14-q21 orders 19 genetic markers in ten intervals Eur J Hum Genet 1994;2;59-65.
37 Cox D, et al.: A linkage map of human chromosome 14 including 12 gene loci. Genomics 1994;in press.
38 Sarfarazi M, Tsipouras P, Del Mastro R, Kilpatrick M, Farndon P, Boxed M, Bridges A, Boileau C, Junien C, Hayward C, Brock D, Child A: A linkage map of 10 loci flanking the Marfan syndrome locus on 15q: results of an international consortium study. J. Med. Genet. 1992;29:75-80.
39 Bowcock AM, Barnes RI, White RL, Kruse TA, Tsipouras P, Sarfarazi M, Jenkins T, Viljoen C, Litt M, Kramer PL, Murray JC, Vergnaud G: The CEPH consortium linkage map of human chromosome 15q. Genomics 1992;14:833-840.
40 Donlon TJ, Beckmann JS, Malcolm S: Genome Priority Reports 1993;1:438-447.
41 Fougerousse F, Broux O, Richard R, Allamand V, de Souza A, Bourg N, Brenguier L, Devaud C, Pasturaud P, Roudant C, Channilkulchai N, Hillaire D, Bui H, Chumakov I, Weissenbach J, Cherif D, Cohen D, Beckmann JS. Mapping of a chromosome 15 region involved in limb girdle muscular dystrophy. J S Hum Mol Genet 1994;3:285-293.
42 Hidebrand CE, Breunig MH, Reeders ST, Callen D: Report of committee on the genetic constitution of chromosome 16 p448-472 Chromosome Coordinating Meeting (1992): Cuticchia AJ, Pearson PL, Klinger HP (eds) Genome Priority Reports vol. 1. Basel Karger, 1993
43 Solomon E, Ledbetter D, Fain P: Report on the genetic constitution of chromosome 17 p473-504 Chromosome Coordinating Meeting (1992): Cuticchia, AJ, Pearson PL, Klinger HP (eds) Genome Priority Reports vol. 1. Basel Karger, 1993.
44 Donis-Keller H, Green P, Helms C, Cartinhour S, Weiffenbach B, Stephens K, Keith TP, Bowden DW, Smith DR, Lander ES et al: A genetic linkage map of the human genome. Cell 1987; 51:319-337.
45 O'Connell P, Lathrop GM, Leppert M, Nakamura Y, Muller U, Lalouel J-M, White R: Twelve loci form a continuous linkage map for human chromosome 18. Genomics 1988;3:367-372.
46 Straub RE, Speer MC, Luo Y, Rojas K, Overhauser J, Ott J, Gilliam TC: A microsatellite genetic linkage map of human chromosome 18. Genomics 1993;15:48-56.
47 Rojas K, Overhauser J: Sublocalization of 21 chromosome 18-specific microsatellite markers. Genomics 1993;18:169-171.
48 Harley HG, Brook JD, Floyd Rundle SA, Crow S, Walsh KV, Thibault M-C, Harper PS, Shaw DJ: Detection of linkage disequilibrium between the Myotonic dystrophy locus and a new polymorphic DNA marker. Am J Hum Genet 1991;49:68-75.
49 Shaw DJ, Harley HG, Brook JD, McKeithan TW: Long range restricton map of a region of human chromosome 19 containing the apolipoprotein genes , a CII - associated break point, and two polymorphic MluI sites. Hum Genet. 1989;83:71-74.

50 Hazan J, Dubay C, Pankowiak MP, Becuwe N, Weissenbach J: A genetic linkage map of human chromosome 20 composed entirely of microsatellite markers. Genomics 1992;12:183-189.
51 Melis R, Bradley P, Elsner T, Robertson M, Lawrence E, Gerken S, Albertsen H, White R: Polymorphic SSR (Simple-Sequence-Repeat) markers for chromosome 20. Genomics 1993;16:56-62.
52 Vergnaud G, Mariat D, Apiou F, Aurias A, Lathrop M, Lauthier V: The use of synthetic tandem repeats to isolate new VNTR loci: cloning of a human hypermutable sequence. Genomics 1991;11:135-144.
53 Loffler C, Rao VVNG, Schnittger S, Pastuszak D, Schubert S, Hansmann I: A first FISH map of human chromosome 20 discloses complete homology with mouse chromosome 2 and assigns candidate mutations. Am J Hum Genet 1993;53:1324.
54 McInnis MG, Chakravarti A, Blaschak J, Petersen MB, Sharma V, Avramopoulos D, Blouin JL, Konig U, Brahe C, Matise TC et al: A linkage map of human chromosome 21: 43 PCR markers at average intervals of 2.5 cM. Genomics 1993;16:562-571.
55 Chumakov I, Rigault P, Guillou S, Ougen P, Billaut A, Guasconi G, Gervy P, LeGall I, Soulare P, Grinas L et al: Continuum of overlapping clones spanning the entire human chromosome 21q. Nature 1992;359:380-387.
56 Bosch A, Nunes V, Patterson D and Estivill X: Isolation and characterisation of fourteen CA-repeat microsatellites from Human Chromosome 21. Genomics 1993;18:151-155.