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PHYSICAL MAPPING OF HUMAN CHROMOSOME 16

Incorporates final report for project *Correlation of Physical and Genetic Maps of Human Chromosome 16* terminated on 01.31.92 and initial report for current project *Physical mapping of Human Chromosome 16* (02.01.92 to 06.31.92)

Grant R. Sutherland

Adelaide Children's Hospital
North Adelaide SA 5006
Australia

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TITLE: Physical mapping of human chromosome 16.

PRINCIPAL INVESTIGATOR: G.R. Sutherland

SENIOR ASSOCIATES: D.F. Callen, J.C. Mulley, R.I. Richards

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One of the project aims for the past year have been to further refine the cytogenetic-based physical map of chromosome 16. This has been achieved by extending the panel of mouse/human hybrids of chromosome 16 to over sixty hybrids and mapping approximately 250 DNA markers, Fig. 1. The high resolution of this physical map, with an average distance between breakpoints of less than 1.6 Mb, and the availability of at least one STS in the majority of these intervals, will be the basis for constructing extensive contigs of cloned DNA.

In collaboration with the Los Alamos National Laboratory, we have mapped cosmid contigs to this high resolution cytogenetic-based physical map. Currently greater than 12% of the euchromatic DNA of chromosome 16 (estimated at 85 Mb) which has been cloned into cosmids, and assembled into contigs, has been physically mapped to this chromosome. The cytogenetic-based physical map will form the basis for closure of the cloned DNA map in 16q22.1. YACs have been isolated (in collaboration with CEPH) at the proximal extremity of 16q22.1 and are currently being assembled into a contig. It is planned to extend this process by use of both the currently mapped STSs and additional STSs isolated from a library constructed by microdissection of this chromosome band.

The aim to produce a synthesis of the physical and genetic linkage maps of chromosome 16 has been achieved, Fig. 2. The majority of DNA markers which have been typed in the CEPH families have now been physically mapped to the chromosome using the hybrid panel.

A CEPH consortium map of chromosome 16 is currently in progress and is being coordinated from our Department.

The (AC)n microsatellite markers which have already been isolated have been distributed to a number of collaborating groups mapping disease genes. These include Prof. M. Gardiner, London (Batten disease); Dr. Mary-Clair King, San Francisco (breast cancer); Dr. Sandra Marles, Winnepeg (lattice corneal dystrophy, type I) and Dr. Daniel Kastner, Bethesda (familial Mediterranean fever).

A cDNA library derived from unprocessed RNA message has been constructed from the somatic cell hybrid CY18 (this contains only chromosome 16) . Identification of human chromosome 16 specific cDNA clones can be undertaken by screening of such a library with total human DNA. Evaluation of this library is presently being undertaken and it is hoped this will be a valuable procedure for isolating human chromosome 16 genes.

The future short-term aims of this chromosome 16 project include the completion of the STS-based genetic map of chromosome 16. The refinement of the cytogenetic-based physical map will continue, with emphasis on mapping STSs from cosmid contigs (in collaboration with Los Alamos), and the development of ESTs (expressed sequence tagged sites). There will be increased emphasis on the isolation and use of YACs to enable the construction of contig maps spanning large regions of this chromosome.

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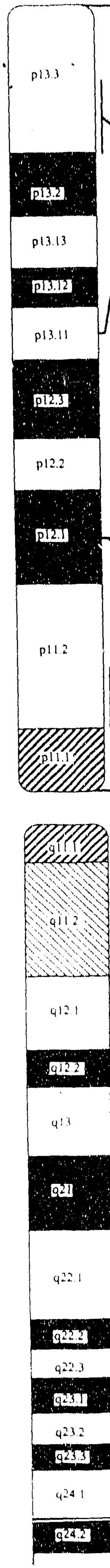
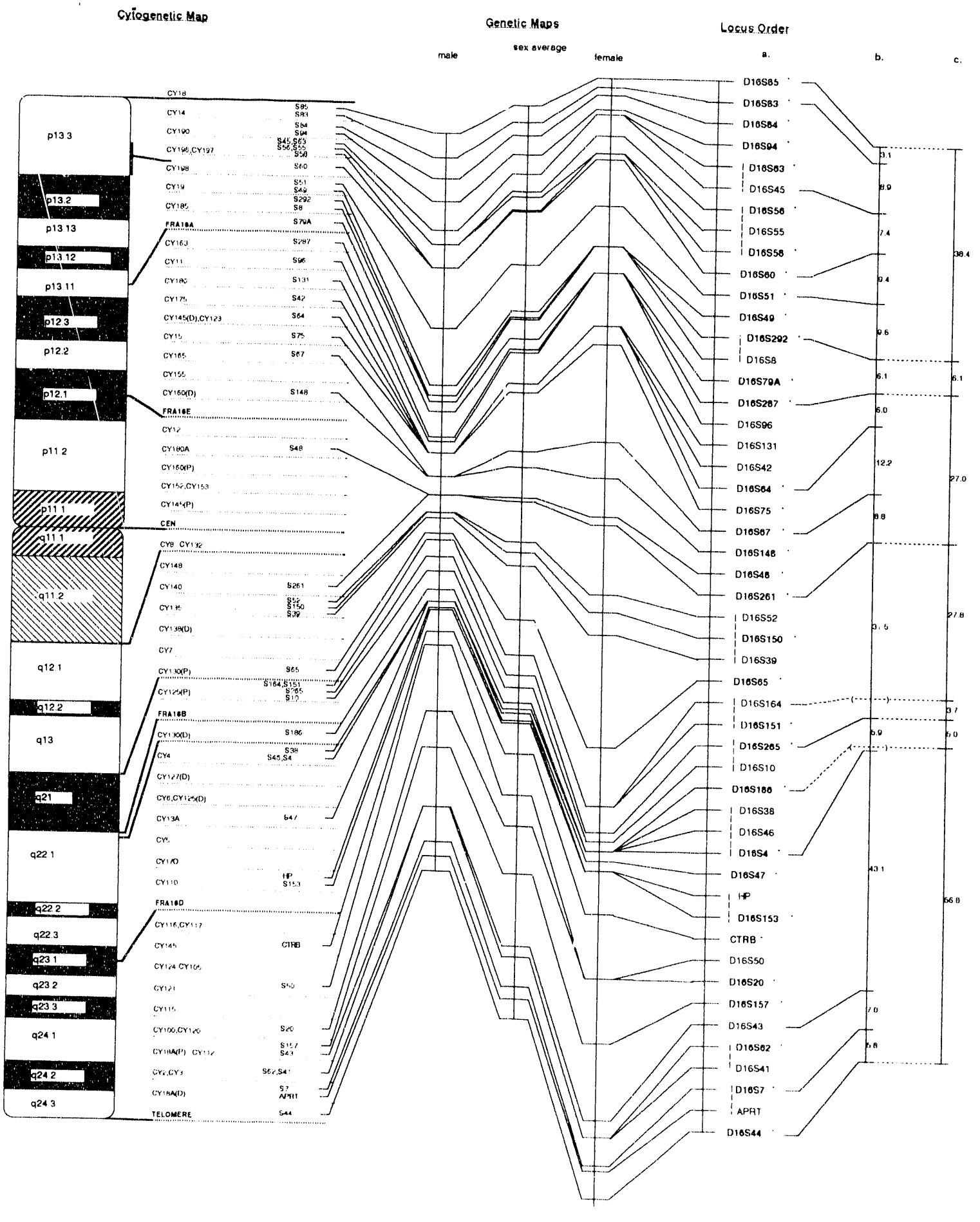
FIG. 1. **Cytogenetic-based physical map of human chromosome 16.** The portion of chromosome 16 present in each mouse/human hybrid cell line is delineated by a horizontal line with an arrow indicating the direction of the retained portion of chromosome 16 from the breakpoint. Breakpoints of fragile sites are indicated by horizontal arrows. The majority of hybrid cell lines contain the portion of chromosome 16 from the breakpoint to the tip of the long arm (qter) and have been derived from translocations involving chromosome 16. Exceptions are five interstitial deletions (CY125, CY127, CY130, CY138, CY160); the hybrid CY18, which contains an intact chromosome 16; the hybrid CY180, which was derived from an insertional translocation of 16p13 into 11q; and CY18A and CY145, which contain one and two fragments of 16, respectively. The relative sizes of the idiograms for the short and long arms are not to scale. Hybrids CY2 and CY3 contain the der(X) and the der(16), respectively, from the same t(X;16) translocation. DNA markers are divided into columns corresponding to genes, cosmids that have been assembled into contigs by repetitive sequence fingerprinting and oligonucleotide primers that flank (AC)n microsatellite repeats by the Los Alamos National Laboratory, and other anonymous DNA markers. When such (AC)n repeats have been identified in previously mapped DNA markers, the location of these markers is also given. All genes, cosmids or other DNA markers that have been converted to STS format by synthesis of oligonucleotide primers, are indicated by #. All polymorphic markers that have been typed in the CEPH pedigrees are indicated by *. The D numbers are abbreviated, e.g. *D16S3* to *S3*, and DNA marker names are given in brackets. *In situ* hybridixation to prophase banded chromosomes provided additional links between the ordered panel of hybrid breakpoints and the idiogram. The location of the hybridization signal as indicated by a vertical line.



HYBRIDS	GENES	FINGERPRINTED COSMIDS	MICROSATELLITE REPEATS	DNA MARKERS - OTHER
CY18↓				S21(FR3.42) S85(3HVR)*
CY14↓	HBA # MPG #	(c77E8)	S94(ACVK5)* S291(16AC2.5)*	S94(VK5) #* S125(26-6)
23HA↓			(16AC8.15)	
CY190↓		S355(c28D3) S387(c311E7)		S45(CRI-090)* S55(CRI-0128)* S56(CRI-0129)* S58(CRI-0133)* S63(CRI-0327)* S80(24.1) S81(3.15) S93(VK15)
CY196↓CY197↓		S338(c10B8) S340(c49E7) S354(c30C1)#		S60(CRI-0136)* S143(16-116)
CY198↓	PRM1 #	S334(c14B8)# S360(c52C5)# S365(c54A6)#		S33(16-108) S34(16/55B) S49(CRI-0114)* S51(CRI-120)* S119(2.36) S273(16-14N)
CY19↓		S341(c49D11)# S352(c35B11)# S356(c329F7)# S376(c308B2)#	S292(16AC2.3)*	S8(ACHF1)* S32(16-118)* S130(VK43)
CY185↓		(c305F6)	(16AC7.22)	S79A(36.1)*# S92(16/125B)
CY183↓ FRA16A →			S287(AC16XE81)*	S287(16XE81)#
CY163↓		(c13H1)#		S96(VK20)*# S79B(36.1)*# S36(16-12)
CY11↓		(c40A7)#		S131(VK45)* S325(T301)#
CY180↓		S370(c25H11)#		S42(CRI-066)*
CY175↓				S64(CRI-0373)*
CY145(D)↓CY13↓CY123↓		S335(c307G2) (c33H1)#	S293(16AC6.16) S328(SM8)	S75(CRI-R99)* S159(CJ52.94)*
CY15↓	PRKCB1 #	S295(c62F3)#	S294(16AC1)* S295(62F3)* S319(16AC7.14)*	S37(16-02) S67(CRI-0391)* S100(VK8) S129(VK49) (16XE71)
CY165↓		S296(c62B4)#	S296(62B4)*	
CY155↓		S297(c15H1)# S347(c12F8)#	S297(15H1)*	S148(CJ52.95)*
CY160(D)↑	ATP2A1			
FRA16E →	IL4R	S366(c302C7)	S288(16AC7.1) S298(16AC3.12)* S299(16AC6.17)*	S120(1.57) S272(16-129N)
CY12↓	SPN #	S383(c80B3)	(16AC7.59)	S271(16-30N) S48(CRI-0101)* S104(VK35)
CY180A↓	ITGAM #	(c41A3)#		S321(T118)#
CY160(P)↓		S333(c10D7) S346(c19F8) (c302E3)#		S102(VK31)
CY152↓CY153↓CY199↓				S149(CJ52.27)*
CY145(P)↑				S57(CRI-0131)* S103(VK33)
CENTROMERE			S300(16AC1.1)*	
CY8↓CY138(P)↑		S388(c11A11)# (c12E7)#	S302(16AC6.5)	S27(16-5)
CY148↓		S350(c305F10) S361(c47D8) S364(c315F5)#	S261(MFD24)*	S290(T102)#
CY140↓		S150(c59D10)# S336(c71E10) S337(c71C7)# S368(c21E1) S359(c301B3) S372(c304D7) S379(c306H3)# S384(c47G4)# (c307E12)	S304(16AC1.14) S308(16AC1.18)	S39(CRI-03)* S52(CRI-0123)* S150(CJ52.161)* S182(16-91) S270(16-38N)
CY135↓	CLG4A	S374(c47G9)# S390(c10F5) (c32B4)		S175(16-57) S178(16-65)
CY138(D)↓	GNAO1 #		S306(16AC5.4)	S187(16-103)
CY7↓	CETP* MT #*	(c40B1)#	S317(16AC7.9) S320(16AC8.52)	S65(CRI-0377)* S326(T210)#
CY130(P)↑		S378(c30E12) (c306G3) (c5H9)		S10(ACHF3)* S151(CJ52.209)* S185(16-95)
CY122↓		S347(c12F8)# S357(c29E9)#	S164(AC16-15)* S168(AC16-42) S265(MFD23)* S267(MFD65)	S164(16-15)# S168(16-42)# S171(16-47) S177(16-63) (16XE78)
CY125(P)↑CY127(P)↑				S163(16-10)#
FRA16B →			S186(AC16-101)*	S174(16-53)# S186(16-101)#
CY130(D)↓	CAT # APOEL1*		S301(16AC6.21)* S397(MFD98) S398(MFD168)	S4(ACH207)* S38(CRI-02)* S46(CRI-091)* S179(16-67)
CY4↓	LCAT #			S124(1.99) S152(CJ52.1)* S160(CJ52.196)*
CY127(D)↓	GOT # UVO		S318(16AC8.20)	
CY6↓CY125(D)↓				S47(CRI-095)* S269(16-132N) S324(T104)# (16XE61)
CY13A↓	ALDOA # NMOR1 #	(c303F2)#		S322(T117)# S323(T116)#
CY3↓	CALB2 #		S260(MFD12)	S185(16-92)
CY170↓	HP #* TAT	S153(c67G12)#		S153(CJ52.10)* S14(ACH202)
CY110↓		(c80H3)		
FRA16D →				S162(16-98)
CY116↓CY117↓	CTRB*	S342(c312C6)#		
CY145↓		S395(c33G11)#		
CY124↓CY105↓		S348(c301B4) S353(c23E10)#	S269(MFD62)	S50(CRI-0119)* S181(16-87)
CY121↓		S377(c306E12) (c50E11)	S289(16AC7.46)*	S166(16-22)
CY115↓		S344(c16F1) S389(c10B3)		S5(ACH224)* S20(PB-9)* S40(CRI-015)* S176(16-66)
CY100↓CY120↓	COX4	S332(c305D6) S363(c16D9)# S392(c305E9) S393(c301F3) (c58F8)		S43(CRI-084)* S157(CJ52.96)*
CY18A(P)↓CY112↓		S358(c325G11)# (c301B6)# S359(c26E3)#		S41(CRI-043)* S52(CRI-0149)* S154(CJ52.105)*
CY2↓CY3↑	APRT #*		S305(16AC...)	

FIG. 2 **Comprehensive linkage map for chromosome 16.** a. Order of loci with framework loci indicated in bold type (*). Adjacent loci not uniquely ordered by chromosomal breakpoints and/or with likelihood support of less than 1000:1 are indented and indicated by a dotted line. b. Order and distance between those loci with minimum heterozygosity of 60%. c. Position of the 6 PCR based microsatellite markers.


Cytogenetic Map
Genetic Maps
male
sex average
female
Locus Order
a.
b.
c.
p13.3
p13.2
p13.13
p13.12
p13.11
p12.3
p12.2
p12.1
p11.2
p11.1
q11.1
q11.2
q12.1
q12.2
q13
q21
q22.1
q22.2
q22.3
q23.1
q23.2
q23.3
q24.1
q24.2
q24.3
CY18
CY14
CY190
CY196,CY197
CY198
CY19
CY189
FRA16A
CY163
CY11
CY186
CY175
CY145(D),CY123
CY15
CY165
CY155
CY160(D)
FRA16E
CY12
CY180A
CY160(P)
CY152,CY153
CY144(P)
CEN
CY8 CY132
CY148
CY140
CY135
CY138(D)
CY7
CY130(P)
CY125(P)
FRA16B
CY130(D)
CY4
CY127(D)
CY6,CY125(D)
CY13A
CY5
CY10
CY110
FRA16D
CY116,CY117
CY145
CY124 CY106
CY121
CY115
CY100,CY120
CY18A(P) CY112
CY2,CY3
CY18A(D)
TELOMERE
S85
S83
S84
S94
S45,S63
S56,S55
S58
S60
S51
S49
S292
S8
S79A
S267
S96
S131
S42
S64
S75
S67
S148
S48
S261
S52
S150
S39
S65
S164,S151
S265
S10
S186
S38
S45,S4
S47
HP
S153
CTRB
S50
S20
S157
S43
S62,S41
S7
APRT
S44
D16S85
D16S83
D16S84
D16S94
D16S63
D16S45
D16S56
D16S55
D16S58
D16S60
D16S51
D16S49
D16S292
D16S8
D16S79A
D16S267
D16S96
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D16S42
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D16S67
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CTRB
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D16S62
D16S41
D16S7
APRT
D16S44
3.1
8.9
7.4
9.4
9.6
6.1
6.0
12.2
8.8
3.5
3.7
6.9
6.0
43.1
7.0
7.6
38.4
6.1
27.0
27.8
56.0

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