Strategies for Sequencing Human Chromosome 16

FINAL REPORT

by

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This project funded for four years (02.92 to 01.96) was a renewal of a project funded for 2.5 years (07.89 to 01.92). This report covers the period 07.89 to 07.94. The original project was entitled "Correlation of physical and genetic maps of Human Chromosome 16". The aim over this period was to construct a cytogenetic-based physical map of chromosome 16, to enable integration of its physical and genetic maps. This was achieved by collaboration and isolation of new markers until each bin on the physical map contained a polymorphic marker on the linkage map. A further aim was to integrate all mapping data for this chromosome and to achieve contig closure over band q24.

Hybrid Cell Panel

The first aim was to construct a cytogenetic-based physical map with average bin sizes of 2 Mb by the isolation of naturally occurring rearranged chromosome 16s in mouse/human somatic cell hybrids.

The aim has been exceeded. The panel now consists of 88 hybrid cell lines representing 95 independently ascertained breakpoints on the chromosome. With the four fragile sites these divide the 85 Mb of euchromatin into 96 bins of average size 890 kb. There are four breakpoints in the 15 Mb of centromeric heterochromatin. Cloned DNA markers or STSs have been identified in 85 bins.

Subsets of the hybrid panel have been deposited in NIGMS cell repository and made available to our primary collaborators at LANL and numerous groups interested in specific regions of this chromosome and other chromosomes represented in the panel. The current state of the hybrid panel is shown in Fig. 1. This is the highest resolution cytogenetic-based physical map of any autosome.

Correlation of physical and genetic maps

During the initial stages of this project all available polymorphic markers typed on the CEPH panel of families were placed on the physical map. Gaps were targetted in the linkage map and closed by isolation and genotyping of additional PCR-based markers on these families. This resulted in the construction of a PCR-based linkage map which incorporated our 49 markers and 22 markers characterised by other laboratories, including those of the Weissenbach group. We coordinated the production of the CEPH consensus linkage map of this chromosome incorporating all PCR and non-PCR markers at this time. This linkage map has an average marker distance of 2.8 cM and the largest gap is 11.2 cM. This already exceeds the revised 5-year Research Goal of the US Human Genome Project to have a 2-5 cM genetic map completed by 1995. We have continued to integrate available microsatellite markers into the physical map and have now mapped many of the tri- and tetra-nucleotide markers.

Gene and Expressed Sequence Map

We have placed priority on the integration of genes and expressed sequences into the physical map of this chromosome. This has been achieved by mapping all available expressed sequences and cloned genes from published sources, databases and unpublished data obtained as a result of our numerous collaborations. The map now includes 83 genes,

150 expressed sequences, and 185 microsatellite markers and an updated version of this map was recently published (8).

Contig Construction

Development of an integrated mega-YAC, sorted chromosome 16 YAC and cosmid contig map of the chromosome by LANL with our collaboration has now been largely finalised and was published in the Nature Genome Directory (11).

We provided the somatic cell hybrid (CY18) from which chromosome 16 could be sorted to construct the cosmid library, the YACs were mapped by reagents which were first localised by us or LANL to our somatic cell hybrid panel and we provided some primers for STSs developed here to aid contig construction. We constructed the genetic maps for contig orientation and validation of the physical mapping of polymorphic markers.

The generation of sequence ready reagents, that is high resolution cosmid contigs for the region of 16q24, was initiated but could not be completed due to the cessation of funding.

Publications including work which was funded in full or in part by DOE contract DE-FG02-89ER60863

1. Aksentijevich, I., Pras, E., Gruberg, L., Shen, Y., Holman, K., Helling, S., Prosen, L., Sutherland, G.R., Richards, R.I., Ramsburg, M., Dean, M., Pras, M., Amos, C.I., Kastner, D.L. Refined mapping of the gene causing familial Mediterranean fever by linkage and homozygosity studies. *Am. J. Hum. Genet.* (1993) 53: 451-461.
2. Aksentijevich, I., Pras, E., Gruberg, L., Shen, Y., Holman, K., Helling, S., Prosen, L., Sutherland, G.R., Richards, R.I., Dean, M., Pras, M., Kastner, D.L. Familial Mediterranean Fever in Moroccan Jews: Demonstration of a founder effect by extended haplotype analysis. *Am. J. Hum. Genet.* (1993) 53: 644-651.
3. Aksoy, I.A., Callen, D.F., Apostolou, S., Her, C., Weinshilboum, R.M. Thermolabile phenol sulfotransferase gene (STM): Localization to human chromosome 16p11.2. *Genomics* (1994) (In Press).
4. Austruy, E., Jeanpierre, C., Antignac, C., Whitmore, S.A., van Cong, N., Bernheim, A., Callen, D.F., Junien, C. Physical and genetic mapping of the dipeptidase gene DPEP1 to 16q24.3. *Genomics* (1993) 15: 684-687.
Baker, E., Guo, X.H., Orsborn, A.M., Sutherland, G.R., Callen, D.F., Hopwood, J.J., Morris, C.P. The Morquio A syndrome (mucopolysaccharidosis IVA) gene maps to 16q24.3. *Am. J. Hum. Genet.* (1993) 52: 96-98.

5. Breuning, M.H., Snijdwint, F.G.M., Brunner, H., Verwestm A., Ijdo, J.W., Saris, J.J., Dauwerse, J.G., Blonden, L., Keith, T., Callen, D.F., Hyland, V.J., Xiao, G.H., Scherer, G., Higgs, D.R., Harris, P., Achner, L., Reeders, S.T., Germino, G., Pearson, P.L., van Ommen, G.J.B. Map of 16 polymorphic loci on the short arm of chromosome 16 close to the polycystic kidney disease gene (PKD1). *J. Med. Genet.* (1990) 27: 603-613.
6. Callen DF, Thompson AD, Shen Y, Phillips HA, Richards RI, Mulley JC, Sutherland GR. Incidence and origin of "null" alleles in the (AC)_n microsatellite markers. *Am J Hum Genet* (1993) 52: 922-927.
7. Callen, D.F., & Doggett, N.A. : Report of the genetic constitution of chromosome 16 in Human Gene Mapping, 1994 : A Compendium ed. A.J. Cuticchia. John Hopkins Uni Press.
8. Callen, D.F., Doggett, N.A., Stallings, R.L., Chen, L.Z., Whitmore, S.A., Lane, S.A., Nancarrow, J.K., Apostolou, S., Thompson, A.D., Lapsys, N.M., Eyre, H.J., Baker, E.G., Shen, Y., Holman, K., Phillips, H., Richards, R.I., Sutherland, G.R. High-resolution cytogenetic-based physical map of human chromosome 16. *Genomics.* (1992) 13: 1178-1185.
9. Callen, D.F., Eyre, H., Lane, S., Shen, Y., Hansmann, I., Spinner, N., Zackai, E., McDonald-McGinn, D., Schuffenhauer, S., Wauters, J., Van Thienen, M.-N., Van Roy, B., Sutherland, G.R., Haan, E.A. High resolution mapping of interstitial long arm deletions of chromosome 16: relationship to phenotype. *J. Med. Genet* (1993) 30: 828-832.
10. Callen, D.F., Lane, S.A., Kozman, H., Kremmidiotis, G., Whitmore, S.A., Lowenstein, M., Doggett, N.A., Kenmochi, N., Page, D.C., Maglott, D.R., Nierman, W.C., Murakawa, K., Berry, R., Sikela, J.M., Houlgatte, R., Auffray, C., Sutherland, G.R. Integration of transcript and genetic maps of chromosome 16 at near-1-Mb resolution : demonstration of a "hot-spot" for recombination at 16p12. *Genomics* (1995) 29: 503-511.
11. Ceccherini, I., Romeo, G., Lawrence, S., Breuning, M.H., Harris, P.C., Himmelbauer, H., Frischauf, A.M., Sutherland, G.R., Germino, G.G., Reeders, S.T., Morton, N.E. Construction of a map of chromosome 16 by using radiation hybrids. *Proc. Natl. Acad. Sci. USA* (1992) 89: 104-108.
12. Chen, L.Z., Harris, P.C., Apostolou, S., Baker, E., Holman, K., Lane, S.A., Nancarrow, J.K., Whitmore, S.A., Stallings, R.L., Hildebrand, C.E., Richards, R.I., Sutherland, G.R., Callen, D.F. A refined physical map of the long arm of human chromosome 16. *Genomics* (1991) 10: 308-312.
13. Chen, L.Z., Shen, Y., Holman, K., Thompson, A., Lane, S., Richards, R.I., Sutherland, G.R., Callen, D.F. An STS at the D16S290 locus. *Nucl. Acids Res.* (1991) 19: 5793.

14. Cleton-Jansen, A.M., Moerland, E.W., Kuipers-Dijkshoorn, N.J., Callen, D.F., Sutherland, G.R., Devilee, P., Cornelisse, C.J. At least two different regions are involved in allelic imbalance on chromosome arm 16q in breast cancer. *Genes Chromo Cancer* (1994) 9: 101-107.
15. Doggett, N., Callen, D. Report of the Third International Workshop on Human Chromosome 16 Mapping 1994. *Cytogenet. Cell Genet* (1995) 68: 165-184.
16. Doggett, N.A., Callen, D.F., Chen, Z.L., Moore, S., Tesmer, J.G., Duesing, L.A., Stallings, R.L. Identification and regional localization of a human IMPD-dehydrogenase-like locus (IMPDHLI) at 16p13.13. *Genomics* (1993) 18: 687-689.
17. Doggett, N.A., Goodwin L.A., Tesmer, J.G., Meincke, L.J., Bruce, D.C., Clark, L.M., Altherr, M.R., Ford, A.A., Chi, H.-C., Marrone, B.L., Longmire, J.L., Lane, S.A., Whitmore, S.A., Lowenstein, M.G., Sutherland, R.D., Mundt, M.O., Knill, E.H., Bruno, W.J., Macken, C.A., Torney, D.C., Wu, J.R., Griffith, J., Sutherland, G.R., Deaven, L.L., Callen, D.F., Moyzis, R.K. An integrated physical map of human chromosome 16. *Nature* (1995) 377: 335-365.
18. Hildebrand, C.E., Breuning, M.H., Reeders, S.T., Callen, D.F. (1993) Report of the committee on the genetic constitution of chromosome 16. Chromosome Coordinating Meeting (1992), Cuticchia, A.J., Pearson, P.L., Klingler, H.P. (Eds.) : *Genome Priority Reports*, Vol. 1, Basel, Karger, 1993.
19. Jeanpierre, C., Whitmore, S.A., Austruy, E., Cohen-Salmon, M., Callen, D.F., Junien, C. Chromosomal assignment of the uromodulin gene (UMOD) to 16p13.11. *Cytogenet Cell Genet* (1993) 62: 185-187.
20. Klanke, C.A., Su, Y.R., Callen, D.F., Wang, Z., Meneton, P., Baird, N., Kandasamy, R.A., Orlowski, J., Otterud, B.E., Leppert, M., Shull, G.E., Menon, A.G. Molecular cloning and physical and genetic mapping of a novel human Na⁺/H⁺ exchanger (NHE5/SLC9A5) to chromosome 16q22.1. *Genomics* (1995) 25: 615-622.
21. Kozman, H.M., Gedeon, A.K., Whitmore, S., Suthers, G.K., Callen, D.F., Sutherland, G.R., Mulley, J.C. Addition of MT, D16S10, D16S4 and D16S91 to the linkage map within 16q12.1-q22.1. *Genomics* (1991) 11: 756-759.
22. Kozman, H.M., Keith, T.P., Donis-Keller, H., White, R.L., Weissenbach, J., Dean, M., Vergnaud, G., Kidd, K., Gusella, J., Royle, N.J., Sutherland, G.R., Mulley, J.C. The CEPH Consortium Linkage Map of Human Chromosome 16. *Genomics* (1995) 25: 44-58.

23. Kozman, H.M., Phillips, H.A., Callen, D.F., Sutherland, G.R., Mulley, J.C. Integration of the cytogenetic and genetic linkage maps of human chromosome 16 using 50 physical intervals and 50 polymorphic loci. *Cytogenet. Cell Genet.* (1993) 62: 194-198.
24. Kozman, H.M., Phillips, H.A., Sutherland, G.R., Mulley, J.C. A multipoint genetic linkage map around the fragile site FRA16A on human chromosome 16. *Genet (Life Sci. Adv.)* (1992) 11: 229-233.
25. Liu, P., Siciliano, J., White, B., Legerski, R., Callen, D., Reeders, S., Siciliano, M.J., Thompson, L.H. Regional mapping of human DNA excision repair gene *ERCC4* to chromosome 16p13.31-p13.2. *Mutagenesis* (1993) 8: 199-205.
26. Maglott, D.R., Durkin, A.S., Lane, S.A., Callen, D.F., Feldblyum, T.V., Nierman, W.C. The gene for membrane protein E16 (D16S469E) maps to human chromosome 16q24.3 and is expressed in human brain, thymus, and retina. *Genomics* (1994) 23: 303-304.
27. Mulley, J.C., Sutherland, G.R. Integrating maps of chromosome 16. *Current Opinion Genet. Develop.* (1993) 3: 425-431.
28. Phillips, H.A., Harris, P., Richards, R.I., Sutherland, G.R., Mulley, J.C. Dinucleotide repeat polymorphisms at the D16S164, D16S168 and D16S186 loci at 16q21-q22.1. *Nucl. Acids Res.* (1991) 19: 6964.
29. Phillips, H.A., Hyland, V.J., Holman, K., Callen, D.F., Richards, R.I., Sutherland, G.R. Dinucleotide repeat polymorphism at D16S287. *Nucl. Acids Res.* (1991) 19: 6664.
30. Phillips, H.A., Thompson, A.D., Kozman, H.M., Sutherland, G.R., Mulley, J.C. A microsatellite marker within the duplicated D16S79 locus has a null allele : Significance for linkage mapping. *Cytogenet. Cell Genet.* (1993) 64: 131-132.
31. Pritchard, M.A., Baker, E., Whitmore, S.A., Sutherland, G.R., Idzerda, R.L., Park, L.S., Cosman, D., Jenkins, N.A., Gilbert, D.J., Copeland, N.G., Beckmann, M.P. The interleukin-4 receptor gene (*IL4R*) maps to 16p11.2-16p12.1 in human and to the distal region of mouse chromosome 7. *Genomics* (1991) 10: 801-806.
32. Richards, R.I., Holman, K., Lane, S., Sutherland, G.R., Callen, D.F. Human Chromosome 16 Physical Map : Mapping of somatic cell hybrids using multiplex PCR deletion analysis of sequence tagged sites *Genomics* (1991) 10: 1047-1052.

33. Samani, N.J., Whitmore, S.A., Kaiser, M.A., Harris, J., See, C.G., Callen, D.F., Lodwick, D. Chromosomal assignment of the human SA gene to 16p13.11 and demonstration of its expression in the kidney. *Biochem Biophys Res Comm* (1994) 199: 862-868.
34. Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., Richards, R.I. Six dinucleotide repeat polymorphisms on human chromosome 16q12.1-q24.1. *Hum Molec Genet* (1993) 2: 1505.
35. Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., Richards, R.I. Three dinucleotide repeat polymorphisms on human chromosome 16p13.11-p13.3. *Hum Molec Genet* (1993) 2: 1506.
36. Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., Richards, R.I. Dinucleotide repeat polymorphisms at the D16S525, D16S531 and D16S522 loci. *Hum Molec Genet* (1994) 3: 210.
37. Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R. and Richards, R.I. Five dinucleotide repeat polymorphisms on human chromosome 16q24.2-q24.3. *Hum. Mol. Genet.* (1993) 2: 1504.
38. Shen, Y., Holman, K., Doggett, N.A., Callen, D.F., Sutherland, G.R., Richards, R.I. Four dinucleotide repeat polymorphisms on human chromosome 16. *Hum. Mol. Genet.* (1993) 2: 1745.
39. Shen, Y., Holman, K., Thompson, A., Kozman, H., Callen, D.F., Sutherland, G.R., Richards, R.I. Dinucleotide repeat polymorphism at the D16S288 locus. *Nucl. Acids Res.* (1991) 18: 5445.
40. Shen, Y., Kozman, H.M., Thompson, A., Phillips, H.A., Holman, K., Nancarrow, J., Lane, S., Chen, L.-Z., Apostolou, S., Doggett, N.A., Callen, D.F., Mulley, J.C., Sutherland, G.R., Richards, R.I. A PCR-based genetic linkage map of human chromosome 16. *Genomics* (1994) 22: 68-76.
41. Shen, Y., Thompson, A.T., Holman, K., Callen, D.F., Sutherland, G.R., Richards, R.I. Four dinucleotide repeat polymorphisms on human chromosome 16 at D16S289, D16S318, D16S319 and D16S320. *Hum. Molec. Genet.* (1993) 1: 773.
42. Stallings, R.L., Whitmore, S.A., Doggett, N.A., Callen D.F. Refined physical mapping of chromosome 16 specific low-abundance repetitive DNA sequences. *Cytogenet. Cell Genet.* (1993) 63: 97-101.
43. Thompson, A.D., Shen, Y., Holman, K., Sutherland, G.R., Callen, D.F., Richards, R.I. Isolation and characterisation of (AC)_n microsatellite genetic markers from human chromosome 16. *Genomics* (1992) 13: 402-408.

44. Whitmore, S.A., Apostolou, S., Lane, S., Nancarrow, J.K., Phillips, H.A., Richards, R.I., Sutherland, G.R., Callen, D.F. Isolation and characterization of transcribed sequences from a chromosome 16 hn-cDNA library and the physical mapping of genes and transcribed sequences using a high-resolution somatic cell panel of human chromosome 16. *Genomics* (1994) 20: 169-175.
45. Yasuda, T., Nadano, D., Iida, R., Takeshita, H., Lane, S.A., Callen, D.F., Kishi, K. Chromosomal assignment of the human deoxyribonuclease I gene, DNASE1 (DNL1), to band 16p13.3 using the polymerase chain reaction. *Cytogenet. Cell Genet.* (1995) 70: 221-223.

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