The ultimate goal of the work proposed is to generate and apply novel technologies to speed completion and integration of the human genome map and sequence with biomedical problems. To do this, techniques were developed and genome-wide resources generated. This includes a genome-wide Mapped and Integrated BAC/PAC Resource that has been used for gene finding, map completion and anchoring, breakpoint definition and sequencing.

In the last period of the grant, the Human Mapped BAC/PAC Resource was also applied to determine regions of human variation and to develop a novel paradigm of primate evolution through to humans. Further, in order to more rapidly evaluate animal models of human disease, a BAC Map of the mouse was generated in collaboration with the MIT Genome Center, Dr. Bruce Birren.

1. Mouse BAC Resource

BACs were defined that carry the end markers of the genetic map for each mouse chromosome. Further, about 100 additional markers were defined to provide physical markers throughout mouse metaphase chromosomes for anchor points on the mouse map.

2. Human Variation and the basis of human chromosomal rearrangements

Regions of duplication were defined throughout the human genome by using an analysis of single BACs that yielded more than a single site on fluorescence in situ hybridization. Most exciting was that the sites of putative duplication were found to mirror the sites that in humans, participate most commonly in spontaneously in inversions. This firmly relates genome duplications to rearrangements and provides numerous points at which to study sequences and mechanisms responsible, possibly shedding light on cancers.

3. Human and Primate Evolution

Regions of duplications were found to mirror and likely to originate from in many instances, the sites of inversions that characterize evolution of the primates from Orangutans through Gorilla, Chimpanzee and human. The findings suggested a novel paradigm of human evolution in which inversions are predisposed to by duplications and then, themselves lead to further duplications, some of which contain genes that, when overexpressed, may confer
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selective advantage. The significance of these findings and theoretical considerations is that the genes for evolutionary change, even in higher primates, may be found in the duplicated regions defined by BACs in our study. These BACs then provide reagents for gene analysis and opportunities to define those subsets responsible for cognitive growth.
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