platform presentations in cytogenetics/ education and public health

13

An Integrated BAC/PAC Resource for identifying chromosomal abnormalities in solid tumors. X-N. Chen[1], Z-Y Shi[1], H. Shizuya[2], M. I. Simon[2], B. W. Birren[3], T. J. Hudson[3,4] and J. R. Korenberg[1] [1]Medical Genetics, Cedars-Sinai Medical Center, UCLA, Los Angeles, CA, [2]Div of Biology, Caltech, Pasadena, CA, [3]Whitehead Institute/MIT Center for Genome Research, Cambridge, MA, and [4]Montreal General Hospital Research Institute, McGill University, Montreal, Canada.

Cancer is a single disease and it is a hundred diseases. To understand and treat cancer, we must know the foe: its morphology, its deregulated genes and pathways, and the patterns of chromosomal alterations that are associated with malignant transformation. In order to do this, we need molecular tools to link the visible alterations of clinical disease with the underlying genes and emerging genome sequences. Our laboratory has developed such 'tools' by creating an integrated BAC/PAC Resource for the entire genome by using high resolution fluorescence in situ hybridization (FISH) followed by integration with the genetic, STS and radiation hybrid maps. This resource now covers 30% of the entire human genome, and contains >1,000 STS-linked BACs (Korenberg et al., 1999) and >6,000 mapped BAC/PAC clones.

The goal is to construct an integrated overlapping array of molecular cytogenetic markers that covers 90% of the genome for rapid detection of cancer breakpoints and subtle aneuploidies using a combination of FISH and array technologies. Using this resource, we have already identified an oncogene associated with thyroid tumors (Chen et al, 1998). The ultimate intent will be to define characteristic diagnostic signatures for staged tumors as well as prognostic signatures to sensitively reflect the response to treatment. We propose that the generation of such a resource would best be accomplished by integration of current efforts. This will speed the understanding of cancers and ultimately the treatment of our aging population.

14

Sensitivity of multiple color spectral karyotyping assessed by small constitutional translocations. **Y.S. Fan[1], J. Jung[1], V. Siu[1], and J. Xu[2]. [1]Univ. Of Western Ontario and LHSC, ON, Canada, [2]McMaster Med Ctr, Hamilton, ON, Canada.**

Multiple color spectral karyotyping (SKY) has proved to be a very useful tool for characterization of the complex rearrangements in cancer cells and the de novo constitutional structural abnormalities. The sensitivity of SKY is assessed in this study with 10 constitutional translocations. All of these translocations have involved at least one breakpoint within a single terminal band at the resolution level of 550 bands or within three small terminal bands at the resolution level of 850 bands per haploidy. 9 of 13 small segments involved in the translocations were clearly visualized by SKY, and the origin of the segments were unambiguously identified in 8 of them. Fluorescence in situ hybridizations with subtelomeric probes were performed to determine the reciprocity of the translocations in which a small segment could not be visualized by SKY. Based on the resolution level of G-banding and the information obtained from the FISH analysis, the sensitivity of SKY is estimated to be within approximately 1000-5000 kbp in size. This study has demonstrated the sensitivity, but also the limits of SKY in detecting small interchromosomal alterations with the currently available probes.

15

Cyto 2000 – A Collaborative study for the evaluation of blood chromosome mosaicism. S Schwartz[1] PS Ing[2], DL VanDyke[3], GH Vance[4], JA Reidy[5], SP Caudill[5] ATL Chen[5] and the Cyto 2000 Working Group: [1]Case Western Reserve University; [2]Boys Town Natl Res Hosp; [3]Henry Ford Hospital; [4]Indiana University School of Medicine; [5]Centers for Disease Control and Prevention.

The implications of chromosomal mosaicism have plagued cytogenetics laboratories over the past 40 years. Although this is a frequent phenomena in the clinical cytogenetics laboratory and often misunderstood, there has been little work examining this phenomena. In order to understand better the clinical impact of mosaicism we have undertaken a multi-laboratory survey of mosaicism. We have surveyed 29 laboratories in which over 151,000 stimulated peripheral blood specimens have been studied in a 7-9 year period. A total of 2109 mosaic cases have been identified in these laboratories. Evaluation of this data initially revealed that three different methods of establishing mosaicism was implemented in these labs, although 65% of the labs used the definition of 2 or more cells with trisomy or structural rearrangements and 3 or more cells with monosomy for a specific chromosome. Additionally, 65% of the labs believed that only one culture was needed to establish mosaicism. Among the labs, the range of mosaicism varied between 0.38% and 2.97%, with an overall frequency of 1.39%. Results of the types of mosaicism, revealed that sex chromosomal mosaicism was significantly more common than autosomal mosaicism (64% vs 36%). Overall, half of the sex chromosome mosaicism involved 45,X mosaicism; 45,X/numerical mosaicism was most common (30%) and 45,X/structural mosaicism was slightly less common (20%). Among the autosomal mosaicism, the majority either involved trisomy (mostly chromosome 21) or mosaicism of an accessory marker/ring chromosome. It was interesting to note that 9% of the total mosaic specimens (and 25% of the autosomal cases) involved an autosomal structural mosaic. This is a higher frequency than initially expected.

This survey encompasses the largest group yet studied to explain and understand mosaicism. Results from these studies show that: (1) laboratories do not use uniform criteria to establish mosaicism, and three different criteria were noted in this study; (2) the overall frequency of mosaicism was approximately 1.39%, but there was significant differences between labs; (3) sex chromosome mosaicism was most commonly detected, with the majority involving a 45,X cell line; and (4) autosomal structural mosaicism was more frequent than expected and may have a greater impact than expected. Additional studies are in progress, specifically examining the minimum number of cells needed to establish mosaicism and the effect of ascertainment on the findings. The accumulation of this data will provide a better understanding of the phenomena of mosaicism.

16

Are we making a difference? Genetics in Undergraduate Medical Education. S. A. Goldberg, M. P. Short. American Medical Association, Chicago, IL.

The ASHG and the APHMG have published consensus core curricula for both the basic and clinical science years of undergraduate medical education. Despite wide circulation of these recommendations in the medical literature, how well are the goals of these curricula being met?

Methods: Review of 4 Data sets. 1. Review of clinical clerkship curricula from Chicago area medical schools. 2. Survey of delegates of the Medical Student Section of the American Medical Association (MSS) inquiring when and what of genetics in years M1-M4. 3. Review of the Liaison Committee on Medical Education (LCME) survey of all 125 accredited medical schools '96-'97. 4. Results of the Association of American Medical School exit interview of medical school graduates from 1998 and 1999.

Results:

1. Review of Chicago area clinical clerkship curricula- Genetics is predominantly included in pediatrics and obstetrics and gynecology electives with infrequent appearance in other specialty electives.
2. MSS survey-The majority of genetics education occurs in the first and second year with very little in the M3 and M4 years.
3. 1996-97 LCME survey: This survey looked at the numbers of hours that medical students receive in genetic counseling (3.5 hr), principles of inheritance (6.6 hrs), molecular basis of genetics (15.5hr), and gene therapy (2.0). There is large variation in the amount of time devoted to genetic counseling across the 125 school, with 26 schools who reported no hours at all.
4. AAMC exit interview: The question: Did you receive an appropriate amount of instruction in genetic counseling? 45.8% (1998) and 44.3% (1999) perceived the time spent was inadequate, while 53.2% (1998) and 55.0% (1999) believed it was appropriate, and 1.1% (1998), and 0.7% (1999) said the time spent was excessive.

Conclusion: Current surveys do not adequately assess recognition of consensus recommended curricula. However the four data sets do suggest that genetic education is inadequate, fragmented, and uncoordinated. Recommendations include more concerted efforts to promote adoption of the consensus recommended curricular goals by approaching directors of clinical clerkships by specialty.