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<th>Title</th>
<th>The association of up-regulation of FGF3 and hepatocellular carcinoma metastasis and recurrence</th>
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343 Tumor classification using phylogenetic methods on expression data. A.A. Schuster, R. Doppal, J. Khan. 1) NCBI/NIH/DSHS, Bethesda, MD; 2) NC/NICHD, NIH, DHHS, Gaithersburg, MD.
Tumor classification is a well-studied problem in bioinformatics. Developments in the field of phylogenetics have now made it possible to measure the expression levels of thousands of genes in sample tissue from healthy cell lines or tumors. A number of studies have used the expression of selected genes, or the expression of selected genes in combination with other data, to classify tumors. We apply phylogenetic methods to this problem. We impose a metric on a set of tumors as a function of their gene expression levels, and we seek to infer a tree structure from the distance data, using tree-fitting methods borrowed from the field of phylogenetics. Phylogenetic methods provide a way of imposing a hierarchical relationship on the data, with branch lengths in a phylogeny representing a degree of separation. We demonstrate the flexibility and robustness of the phylogenetic method with regard to resampling methods such as jackknifing and with reproducibility of the real data. Using our methods on a published data set of 87 tissues, comprised mostly of 22 cell lines, round, blue-cell tumors (GSRBCTs), we fit the trees to 87 samples to a pseudo-phylogenetic tree, which readily separated into 4 major clusters corresponding exactly to the four groups of tumors: rhabdomyosarcoma, histoblastic sarcoma, Burkitt's lymphomas, and Ewing's sarcomas. We also test our methods on a set of 22 breast tumors. The resulting tree separated the breast tumors with BRCA1 mutations from those with BRCA2 mutations, with sporadic tumors separated from both other groups and from each other.

344 Differential reduction of qk isoforms in human glioma cell lines. L. Liu, Y. Feng. Emory University, Department of Pharmacology, Atlanta, GA. b.
Cytogenetic alterations at 6q25-26 has been reported to associate with a variety of human malignancies, including glioma. qk expression is known to mediate a role as potential tumor suppressor unclear. The human qk gene (Hsk) has been recently mapped to 6q25-26, encodes a soluble signal transduction protein (QKI), a member of a novel signal transduction activator of RNA (STAR). Three major isoforms of QKI are derived from alternative splicing of the qk primary transcript, which are named QKIs-6, 6 and 7 based on the length of the corresponding mRNA. The role of QKI has been implicated in cell growth, differentiation, as well as apoptosis. In the brain, all QKI isoforms are expressed in various types of glial cells but absent in neurons. We analyzed qk mRNA expression in 23 glioma cell lines. Our preliminary result indicated that around one third of the tumor lines showed significant reduction of the total qk transcripts. Interestingly, qk-7, the isoform that can act as a potent apocopsin inducer, was preferentially reduced. Moreover, qk-6, the isoform that promotes glia differentiation was diminished in most of the glioma cell lines analyzed. In contrast, qk-5, the embryonic predominant isoform remains normal in all the glioma cell lines analyzed. These results suggest that abnormalities of qk alternative splicing may affect glial differentiation and apoptosis, potentially in turn contributes to glioma tumorigenesis.

345 Increased chromosomal instability at common fragile sites in Seckel syndrome. S. Kini, A. A. Casper, A. Devers, B. R. Johnson. Department of Human Genomics, University of Michigan, Ann Arbor, MI.
The partial perturbation of DNA replication induces the expression of common fragile sites. These sites are detected as gaps and breaks on metaphase chromosomes under conditions of replicative stress, such as from aphidicolin treatment or folate deficiency. Replication blocking by aphidicolin, common fragile sites are a constant component of chromosome structure. These sites are often rearranged in tumor cells, and thus are important for understanding the molecular mechanisms of tumors observed in cancer. We have previously shown that ATR, a gene critical to 5 phase and G2/M checkpoint signaling, in response to stalled replication forsi, is crucial for the maintenance of chromosomal stability at common fragile sites. Cells lacking ATR are not viable, making the effects of ATR deficiency challenging to study. Recently, however, a subgroup of patients with Seckel syndrome were found to have a mutation in ATR (Chen et al. Nat Genet 32:497-502 2002) to have a mutation in ATR. Seckel syndrome is a heterogeneous disorder characterized by severe dwarfism, mental retardation, microcephaly, and in some cases, chromosome instability, hematological disorders and leukemias. Two Pakistani families with Seckel syndrome were found to have a silent mutation in ATR that resulted in use of cryptic splice donor sites in exon 5, leading to frameshift and truncation. Homozygous for this homozygous for the hypomorphic allele shows greatly reduced levels of correctly spliced message. We hypothesized that cells from Seckel syndrome patients would have increased instability at common fragile sites, ATR deficient mice, which are consistently affected and three unaffected members of these families. ATR deficiency in all affected individuals was confirmed by western blots. Follow up treatment with aphidicolin, cells homozogous for the hypomorphic allele showed a ~3 fold increase in total gaps and breaks, and in breaks at specific fragile sites, compared to unaffected controls. These results are consistent with our previous findings that ATR deficiency results in increased fragile site instability and suggest that the Seckel syndrome hypomorphic mutation provides a model for studying the biological effects of fragile site instability.

346 The Association of up-regulation of FGFR3 and Hepatocellular Carcinoma Metastasis and Recurrence. X. Gu, K. S. Liu, D. Xue, J. S. Shum, J-M. Wei, W-S. Weng. 1) Department Clinical Oncology, University Hong Kong, Hong Kong, China; 2) Department Pathology, Sun Yat-Sen University, Guangzhou, China; 3) Department General Surgery, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. Hepatocellular Carcinoma (HCC) is one of the most common cancers worldwide with poor prognosis. The poor prognosis of HCC has been associated with the tumor metastasis and recurrence. Therefore, it is imperative to completely understand the molecular mechanisms involved in HCC tumor metastasis in HCC. In the present study, a marker chromosome containing a homogenously staining region (HSR) in a recently established metastatic HCC cell line (H446) was characterized as a specific specific chromosome-specific translocation. The result showed that the HSR was composed of DNA sequence from 11q13. Amplification and overexpression status of CCND1-FGF19-FGF4-FGFR3 gene cluster in H446 in HCC was analyzed by Southern blot and Northern blot hybridization. Amplification and overexpression of CCND1 and FGFR3 were detected. The association of overexpression of FGFR3 and HCC metastasis as well as recurrence was studied using a tissue microarray composed of 60 pairs of primary and paired metastatic HCCs and 30 pairs of primary and matched recurrent HCCs. The results showed that the overexpression frequency of FGFR3 was significantly higher in metastatic HCC (19/40, 47.5%) than that in primary HCC (3/40, 7.5%). Similarly, the frequency of FGFR3 overexpression was significantly higher in recurrent HCC (8/21, 42.8%) than that in primary HCC (1/21, 4.8%). Our results strongly suggested that up-regulation of FGFR3 may play an important role in metastasis and recurrence of HCC.

347 Altered Notch signaling resulting from expression of a WAMPT-MAML2 gene fusion in mucopidermoid carcinomas. F. Enlund, A. Behlouli, Y. Anden, C. Oberg, M. Mark, G. Stenman. 1) Lundmark Laboratory of Cancer Research, Dept of Pathology, Univ Gothenburg, Sweden; 2) Dept of Cell and Molecular Oncogene, Karolinska Institute, Stockholm, Sweden.
Chromosomal translocations in neoplasia commonly result in fusion genes that may encode either new fusion proteins or normal, but ectopically expressed, proteins. Here we report the cloning of a novel fusion gene in a common variant of salivary gland and bronchial gland tumor, mucopidermoid carcinoma (MEC). The fusion, which results from a t(11;19)(q21.23;p13) translocation, creates a chimeric gene in which exon 1 of a novel gene of unknown function, designated WAMPT, is linked to exons 2-5 of the recently identified Mastermind-like Notch coactivator MAML2. In the fusion, the N-terminal basic domain of MAML2, which is required for binding to intracellular Notch (ICD), is replaced by an unrelated N-terminal sequence from WAMPT. Northern blot analysis of RNA isolated from a fusion positive MEC and bronchial gland tumors while MAML2 is expressed in most tissues. The fusion protein was co-localized with both MAML2 and Notch1 ICD to nuclear granules. Analysis of Notch target gene expression profiles in fusion positive MEC and bronchial gland tumors compared to normal salivary gland tissue and MEC lacking the fusion. These findings suggest that altered Notch signaling is an important role in the genesis of new plexus of salivary and bronchial gland origin.

348 Differential Expression of a Gondoblastoma Candidate Gene in Gondoblastoma, Testis and Prostate Cancer Suggests a Role of the Y Chromosome in Human Oncogenesis. Y.-F.C. Liu, H. Lau, Y. L. L.G. Komures, Dept Medicine/VA Med Ctr Univ California, San Francisco, CA. Gondoblastomas on the Y chromosome (G3B) is an oncogenic locus that predisposes the dysgenetic gonads of XY sex-reversed females to tumorigenesis at high frequency. Recent completion of the human Y chromosome (HOMA) project has made it possible to study the entire functional gene content of the Y. From this work, we identified WAMPT (Y chromosome transcribed gene 5) as a candidate gene in prostate, -2 kb in size and from to - from to 9. The abbreviated WAMPT transcripts were abundant in prostate cancer than testis samples. GST pull-down assays demonstrated that all WAMPT proteins were capable of binding to cyclin B. The binding domain was mapped to an N-terminal pentapeptide motif that shares the most significant homology to the oncogene SET. Their preferential expression in cancer, diverse biochemical properties and oncogenic role in prostate carcinoma suggest a role in the multi-step prostate oncogenesis beside its putative oncogenic or tumor-promoting role in gondoblastoma and testicular seminoma.