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Preliminary cytogenetic characterization of an AZT-resistant subclone, clone 5, of the human colon tumor cell line, HCT-15. A. N. Ahsanuddin[1], J. W. Damowski[1,2] and H. F. L. Mark[1,3]. [1]Brown University School of Medicine, [2]Division of Clinical Pharmacology and Lifespan Academic Medical Center Cytogenetics Laboratory[3], Rhode Island Hospital, Providence, RI.

Stage II human trials have indicated that the combination of 3'-azido-3'-deoxythymidine (AZT) with 5-fluorouracil and leucovorin has improved efficacy in the adjuvant chemotherapy of colorectal cancer. The development of resistance to AZT has been well documented in viral metabolism, but has not been fully described in human cells. This renders the drug clinically unpredictable, limiting its chemotherapeutic utility. In order to better study the mechanism of AZT-resistance, we have developed an AZT-resistant colon cancer cell line in culture to serve as a model system.

The human colon adenocarcinoma cell line, HCT-15 (American Type Culture Collection #CCL225), has been previously characterized by conventional cytogenetic studies and by fluorescent *in situ* hybridization (FISH). We have measured the concentration of AZT necessary to inhibit growth by 50% over 5 days (IC_{50}) to be approximately 30 μM. AZT-resistant cell lines were derived by serial passage of HCT-15 cells in increasing concentrations of AZT until stable growth was achieved in 1000 μM AZT. The surviving cell colonies were then subcloned in soft agar. One such cell line, clone 5, was found to have eighty-fold increased resistance to AZT, with an IC_{50} of approximately 2500 μM AZT. We now report a preliminary characterization of the clone 5 cell line in comparison to its parent HCT-15 cell line, using conventional G-banding techniques.

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Epilepsy, genetics, neurotransmitter amino acids and anticonvulsants. N.A. Janjua[1], T. Itano[1], M. Ando[2], and S. Onishi.[2] Departments of [1]Biology and [2]Pediatrics, Faculty of Medicine, Kagawa Medical University, Kagawa, Japan.

One approach to study the genetic and biochemical mechanisms of epilepsy is to undertake family studies involving investigation of candidate biochemical pathways. Using this approach, familial changes in plasma levels of glutamic acid, aspartic acid and taurine have been observed and a genetic basis for these changes has been proposed. However, almost all of these studies have involved patients receiving anticonvulsants thereby raising the possibility that the observed changes could be medication related. To clarify the possible effect of anticonvulsants on neurotransmitter amino acids, we examined plasma levels of these amino acids in patients with and without anticonvulsant therapy. The study group comprised 31 primary generalized epilepsy patients including 24 with and 7 without anticonvulsant treatment. The latter were patients who were investigated either prior to therapy or were not receiving anticonvulsants as they had been seizure free. Amino acid analyses were done on fasting blood samples using an automatic amino acid analyzer. Results showed no significant differences in plasma levels of glutamic acid, aspartic acid and taurine between patients with and without therapy. These findings suggest that plasma neurotransmitter amino acids in epileptic patients may not be altered by anticonvulsants and provide further support to the hypothesis that familial changes in plasma glutamic acid, aspartic acid and taurine in epilepsy have a genetic basis.

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Implications of atypical biochemical data in a case of presumed anencephaly. [1]T Marini, [1]J Sullivan, [2]M Murray, [1]C Kanaan, [1]T Boyd, [1]R Naeem. [1]Baystate Medical Center and the Western Campus of Tufts University School of Medicine, Springfield, MA and [2]New England Medical Center, Boston, MA.

Anomaly scan on a 21 year old primigravida at 22 weeks showed absence of the superior portion of the calvarium with poorly defined cerebral tissue floating in the amniotic fluid. Maternal serum alphafetoprotein (MSAFP) at 18 weeks was 1.4 MOM. The patient was counseled for anencephaly and amniocentesis was performed. Biochemical data consisting of amniotic fluid alphafetoprotein (AFAFP) of 1.94 MOM with weak positive acetylcholinesterase (ACHE) was atypical of classic anencephaly; karyotype was 46,XX. Following termination, fetopsy showed a gaping cranial defect with protruding brain tissue, partially covered by attenuated translucent skin; meninges were torn and congested. Amniotic bands were identified explaining the cranial findings. Radial aplasia and imperforate anus further suggested VATER. While normal MSAFP can be seen with anencephaly, a normal AFAFP and weak positive ACHE are atypical. In the context of the post-mortem findings, it is presumed that without pregnancy termination, expansion of the cranial anomaly would have eventually lead to unequivocally abnormal biochemical results. This case suggests that alternative etiologies, in particular amniotic bands, be considered when atypical biochemical data is seen at midtrimester in the presence of apparent anencephaly.

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Mosaicism in Lowe syndrome. R.L. Nussbaum[1], B.M. Orrison[1], K.E.C. Meyers[2], A. Caputo, and R.A. Lewis[3]. [1] NHGRI, Bethesda, MD, [2]Children's Hospital of Philadelphia, PA, and [3]Baylor College of Medicine, Houston, TX.

In many X-linked and autosomal disorders, the absence of a mutation in the parents of an isolated affected child with a known mutation is still compatible with a significant recurrence risk because of parental mosaicism. Mosaicism has always been a theoretical possibility in Lowe Syndrome but has not been demonstrated to date. Proband LS-54, an isolated patient with Lowe syndrome, is hemizygous for a C→T transition in exon 18 which converts arginine to a stop at position 678 of the OCRL1 gene. The mutation is readily detectable because it creates an additional DdeI site within exon 18. Analysis of his mother's DNA obtained from peripheral blood leukocytes (PBL) revealed no mutation. Surprisingly, however, slit lamp examination of her lens by two independent observers revealed numerous micropunctate opacities distributed in a pattern characteristic of the carrier state for Lowe syndrome. Mutation analysis repeated on fresh samples of PBL DNA from the proband and his mother as well as on buccal scraping (BS) DNA from his mother confirmed the R678X mutation in the proband and its absence in DNA from both PBL and BS DNA in his mother. We interpret these results as indicating the mother is a likely somatic and germline mosaic for the mutation. Genetic counseling for Lowe Syndrome must take mosaicism into account when a DNA sample from the mother of an isolated case fails to demonstrate the mutation seen in an affected child.