829 PILI TORTI AND SENSORINEURAL HEARING LOSS - AN AUTOSOMAL RESESSIVE DISORDER? Marybeth Hummel and Boris G. Kousseff (Spon. by Lewis A. Barness), College of Medicine, University of South Florida, Department of Pediatrics, Tampa.

Pili torti is a congenital anomaly of the hair shaft which is flattened and twisted. The anomaly can exist as an isolated defect or in combination with other hair shaft defects and/or anomalies of other organs. Patients with Menkes syndrome, ectodermal dysplasias, and trichothiodystrophies may have pili torti. In 1965, Björnstad reported five patients with sensorineural hearing loss and pili torti. Several other reports described similar patients. The etiology and genetics of the syndrome however have remained unclear. We report a brother and sister with pili torti and severe bilateral sensorineural hearing loss; the latter became apparent at 3 years of age. Both had almost total alopecia during preteen years. Subsequently they acquired a stubble of dry, brittle scalp hair. Axillary and pubic hair was normal. There was no evidence of hypogonadism or mental retardation.

With no one else in the family having a hearing loss or pili torti, this sibship supports autosomal recessive inheritance for Björnstad syndrome.

● 830 MOLECULAR STUDY OF MUTANT MEDIUM CHAIN ACYL-CoA DEHYDROGENASE IN CULTURED FIBROBLASTS FROM PATIENTS WITH MEDIUM CHAIN ACYL-CoA DEHYDROGENASE DEFICIENCY. Yasuyuki Ikeda*, Susan M. Keese*, Paul M. Coates+ & Kay Tanaka*. *Dept. of Hum. Genet., Yale Univ. Sch. of Med., New Haven, CT, and +Children's Hospital of Phil., Philadelphia, PA (Spon. by W. Roy Breg).

We prepared monospecific antiserum in rabbits against medium chain acyl-CoA dehydrogenase (MCAD) purified from rat liver, and studied the biosynthesis of MCAD in 10 cultured skin fibroblast lines from patients with inborn MCAD deficiency. Cells were incubated with [^{35}S]methionine. The labeled MCAD was immunoprecipitated using the anti-MCAD antiserum and Staph A cells and analyzed by SDS-PAGE. We first demonstrated that anti-rat MCAD antibody cross reacted specifically with human MCAD. MCAD is 1-6 kd larger than four other acyl-CoA dehydrogenases such as isovaleryl-CoA- short chain-, long chain-, and 2-methyl-branched chain acyl-CoA dehydrogenases, and can be readily distinguished from other enzymes by its molecular size on slab SDS-PAGE. It is interesting to note that human MCAD is 1 kd larger than rat MCAD, while there were no differences in molecular size between other human acyl-CoA dehydrogenases and the rat counterparts. In all 10 MCAD deficient lines tested, the MCAD activity ranged from 6-13% of the mean of normal control, but the mutant MCAD in all of these cells were indistinguishable from the normal human MCAD on the basis of molecular size, indicating that all the mutant MCAD's are due to point mutation. This is in contrast to the extensive heterogeneity observed in isovaleryl-CoA dehydrogenase in isovaleric acidemia cells.

● 831 MOLECULAR HETEROGENEITY OF ELECTRON TRANSFER FLAVOPROTEIN (ETF) IN GLUTARIC ACIDURIA TYPE II DUE TO AN ETF DEFICIENCY. Yasuyuki Ikeda, Susan M. Keese, and K. Tanaka. Yale Univ. Sch. of Med., New Haven, CT (Spon. by W. Roy Breg).

Glutaric aciduria type II (GAII) is due to a deficiency of either ETF or ETF dehydrogenase. We studied the biosynthesis of ETF in 10 GAII lines as well as in normal controls. Cells were labeled with [^{35}S]methionine in the presence and absence of rhodamine 6G. Rhodamine 6G inhibits mitochondrial ATP synthesis, thereby inhibiting post-translational processing of the nuclear coded mitochondrial enzymes. The labeled human ETF was immunoprecipitated from the solubilized cells using the anti-rat ETF antiserum and Staph A cells and analyzed by SDS-PAGE. In normal cells, α-subunit is synthesized as a precursor (35 kd), 3 kd larger than the mature counterpart (32 kd), while β-subunit is synthesized in a size indistinguishable from that of the mature β-subunit (27 kd). ETF abnormality was found in three GAII lines. In two of them, α-subunit was synthesized either not at all or in an extremely small amount. The size of the precursor and mature forms of ETF were of the normal sizes. In contrast, α-subunit synthesized in the third GAII line was 1 kd smaller than the normal size, both as precursor and mature form. In all other 7 GAII lines, the synthesis of α-subunit were normal. These 7 cell lines are due to an ETF dehydrogenase deficiency. Abnormality of β-subunit was found in none of the cell lines tested.

● 832 FOLINIC ACID (FA) THERAPY IN DIHYDROPTERIDINE REDUCTASE DEFICIENCY (DHPRD). Mira Irons, Philip J. Langlais, and Harvey L. Levy, Harvard Medical School, Children's Hospital, Depts. of Neurology and Pediatrics; McLean Hospital, Boston.

DHPRD causes hyperphenylalaninemia and reduction of neurotransmitters (NT) due to tetrahydrobiopterin (BH_4) deficiency. Past attempts at therapy have included replacement of NT, BH_4, or both. Therapy with FA, in addition to NT, resulted in an encouraging clinical outcome in two DHPRD siblings (AJHG 36:13S, 1984). We now report studies of the use of FA (25mg daily) alone in a 9 year old patient who failed conventional NT therapy and who has profound neurologic impairment. Within several weeks he became more alert and his seizure frequency diminished. CSF NT metabolite levels (ng/ml) were as follows:

	MHPG	NE	DA	5-HIAA	HVA
Pre-Rx	2.2	ND	ND	0.48	5.1
3 mo. Rx	0.45	0.80	0.45	0.47	3.0
5 mo. Rx	ND	2.4	0.24	1.2	3.5
Normal values	11.2±1.2	0.15-0.30	---	96.4±10.3	120.1±18.6

Thus, CSF norepinephrine (NE) and dopamine (DA) increased, while MHPG and HVA (NE and DA metabolites) declined. There was no clear trend in 5-HIAA (the serotonin metabolite). FA seems to be clinically beneficial in DHPRD. This may be related to an increase in the level of CNS catecholamine NT. This increase may result from either stimulation of NT synthesis by FA, or perhaps more likely, reduction in NT degradation through MAO inhibition by FA

833 EVALUATION OF GENETIC COUNSELING FOLLOWING THE BIRTH OF A MALFORMED NEWBORN. Elizabeth J. Ives, Patricia Henick, Kenneth Morgan, T. Mary Holmes. University of Alberta, Department of Pediatrics, Edmonton, Canada.

The benefits of routine genetic counseling (GC) in ameliorating the family impact of a malformed newborn were investigated by a comparison of 2 Saskatchewan cities Saskatoon (S) and Regina (R). During 33 months all newborns in S and R having a significant malformation were ascertained. (S 122, R 130). A questionnaire (Q), State Trait Anxiety Inventory (STAI) and Family Unit Inventory (FUI) were administered at home to parents of both groups 6 weeks following the birth (T1). S parents only were offered GC which 112 accepted. STAI and FUI were administered again to S and R parents at 6 months (T2), and 1 year (T3). 110 S and 112 R parents were followed to T3. The malformation groups were, with minor exceptions, comparable S v. R. Group comparison of all other variables individually revealed no significant differences S v. R. The impression that GC conferred no particular benefit to families was therefore further explored by development of a family vulnerability index derived by grouping scores from different combinations of variables. Similarly vulnerable S and R families were compared for change in parental anxiety and FUI scores and knowledge of both reproductive risks and the child's condition. Factors influencing response to GC include survival v. demise of the infant, more severe malformation, availability of prenatal diagnosis, lower parental education and income, single mother, parental age difference and certain FUI characteristics. Identification of situations where GC adds significantly to regular management may permit a more appropriate allocation of this limited resource.

△ 834 STABILITY OF GENE TRANSFER IN LESCH NYHAN CELLS. Douglas J. Jolly,[1] Randall C. Willis,[2] and Theodore Friedmann,[1] University of California, San Diego, Departments of Pediatrics[1] and Medicine,[2] La Jolla.

One theoretical criterion for effective and efficient gene therapy for human genetic disease is stability of a functional gene transferred into defective cells. We are studying the deficiency of hypoxanthine guanine phosphoribosyl transferase (HPRT) in the Lesch Nyhan disease as a model system for the development of methods for gene therapy, and have used retroviral vectors to introduce a functional wild-type human HPRT gene into cultured cells derived from Lesch Nyhan patients. Recipient cells express the foreign gene to a variable extent and demonstrate partial phenotypic reversion of several parameters of aberrant purine biosynthesis characteristic of enzyme-deficient cells. Cells grown without selection and revertants to the HPRT-negative phenotype show the continued presence, loss or rearrangement of the foreign gene and of sequences derived from the vector. The introduction of the HPRT gene into random cellular sites by means of some retroviral vectors therefore clearly leads to variability not only in the degree of gene expression but also in its stability, and we conclude that in the presence or absence of selection pressure, the expression and stability of the newly introduced gene depend on the site of integration into the host cell genome.