GENETICS 247A

REVENTION OF NEONATAL HYPERAMMONEMIA IN CITRULLINEMIA. Steven M. Donn, Jess G. Thoene, Golder N. Wilson, University of Michigan Medical Center, Dept. of Pediatrics, Sections of Newborn Services, Genetics, and Metabolic Disease, Ann Arbor.

Citrullinemia, a rare urea cycle enzymopathy (UCE) due to the absence of argininosuccinate synthetase, is characterized by fulminant hyperammonemia and its associated complications. Recent studies have demonstrated alternative means of waste-nitrogen disposal utilizing both urea cycle intermediates and non-urea cycle pharmaceuticals in patients with UCE. Poor neurologic outcome has also been shown to occur with prolonged neonatal hyperammonemia coma. Prevention of

occur with prolonged neonatal hyperammonemia coma. Prevention of hyperammonemia is therefore, a primary goal in the initial treatment. We treated a 3.72 kg term male infant whose citrullinemia had been diagnosed by maternal amniocentesis because of a previously affected sibling who had died at 9 days of age. For this infant we instituted immediate neonatal therapy using 4 mM/kg/d of arginine hydrochloride as a continuous intravenous infusion, begun at two hours of age. Postnatal amino acid concentrations remained between 24 and 91 µMol/L even with protein intake as high as 2.0 g/kg/d. The patient remained neurologically asymptomatic and was successfully switched to oral arginine and ornithine and sodium benzoate therapy at one week of age. He was discharged at 14 days of age on the same medications and a diet consisting of commercial formula to provide 1.8 g/kg/d of protein, with additional caloric supplementation by a

protein-free formula.

Though the long-term prognosis for this infant is unknown, avoidance catastrophic neonatal hyperammonemia in citrullinemia appears achievable.

The Human Type II collagen gene in achonoroplasia. Charis E.L. Eng, and Charles M. Strom (Spon. by Lawrence M. Gartner). University of Chicago, Pritzker School of Medicine, Dept. of Pediatrics, Chicago, IL 60637.

Type II collagen is the predominant collagen of cartilage. This study determines the cause of the HindIII 7 kb (usual, 14 kb), polymorphic band and investigates its application to linkage analyses in achondroplasia. The pertinent restriction sites present in the isolated lambda genomic clones were mapped. Southern filters of HindIII/EcoRI sequential digestions of DNA from individuals with the 7/7, 7/14 and 14/14 HindIII genotypes hybridized to pgHCol(II)A established that the 7 kb band is due to the presence of a new HindIII site 7 kb upstream from the 3' end of pgHCol(II)A. The distribution of the HindIII genotypes in 23 achondroplasts differed from that of the normal population. The gene frequencies of the 7/7, 7/14 and 14/14 genotypes are 0.35 (normal population 0.13), 0.35 (0.52) and 0.30 (0.35). The observation suggests that the HindIII genotypes segregate differently in the population of achondroplasts than in the normal population and may suggest a relationship between the type II collagen gene and achondroplasia. Segregation of the HindIII polymorphic site was analyzed in 9 families with achondroplasia. These families were uninformative. Polymorphic restriction sites in the type II collagen gene should prove useful in linkage analyses of achondroplasia and other diseases which segregate with chromosome 12. (Supported by March of Dimes, AM-33910 and HD-04583). HD-04583).

A Y CENTROMERE REPEAT FOR SEXING FETAL DNA. 819
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Paracentromeric regions of the Y chromosome are essential for determining maleness. Thus DNA probes from this portion of the human Y are preferable for fetal sexing to probes from the heterochromatic, nonessential long arm of the Y. The highly repetitive sequences found at the centromeres of human chromosomes belong to the alphoid repeat family. We have identified human Y cosmids (prepared by cloning DNA from 3E7, a human-mouse hybrid containing Y chromosomes as the only human contribution, and selecting colonies hybridizing to human female genomic DNA) containing the Y alphoid repeat by screening the collection of cosmids with a known alphoid repeat. The sequence found was shown to be Y centromeric by in situ hybridization to metaphase chromosomes and by somatic cell hybrid mapping. Although crosshybridization to other chromosomes occurs on in situ hybridization (at high stringency, there are 5 times as many grains on the Y as on any other chromosome), restriction enzyme analysis of genomic DNAs disclosed that an EcoRI, 5.3 kb fragment is diagnostic of the Y alphoid sequence. Dosage experiments demonstrated 100 copies of this Y-specific alphoid repeat per Y chromosome. The diagnostic Y chromosomal fragment could be rapidly detected in 50 nanograms of DNA. Thus, this probe will provide prenatal sexing of phenotypic males even in the absence of an intact Y chromosome. chromosome.

ADDITIONAL RESTRICTION FRAGMENT LENGTH POLYMORPHISMS (RFLPs) FOR DETECTION OF ORNITHINE TRANSCARBAMYLASE

ADDITIONAL RESIRCTION FRAGMENT LENGTH POLYMORPHISMS (RFLPs) FOR DETECTION OF ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY. Joyce Fox, Rima Rozen, Wayne Fenton, A. Horwich, Leon E. Rosenberg. Yale Univ. Sch. of Med., Departments of Human Genetics and Pediatrics, New Haven, CT.

OTC is a hepatic urea cycle enzyme encoded on the X-chromosome. Human OTC deficiency generally results in lethal neonatal ammonia intoxication in hemizygous affected males. Using an almost full length human OTC cDNA as probe, we have previously identified by Southern blotting two RFLPs following digestion with the endonuclease Msp I. 69% of control females were heterozygous for one or both polymorphisms. To increase the opportunity for prenatal diagnosis of females heterozygous for OTC deficiency, we now report two other RFLPs at the OTC locus. Genomic DNA from 27 control females was digested with Taq I. Three women (11%) were heterozygous for a new RFLP characterized by polymorphic bands at 3.6 and 3.7 kbp. Using the enzyme Bamh I, screening of genomic DNA from 16 women revealed that eight (50%) were heterozygous for another RFLP characterized by polymorphic bands at 18 and 5.2 kbp. No RFLPs were detected when control DNA was digested with 4 other endonucleases. Because each of these RFLPs segregate independently, we estimate that ~85% of OTC carriers can now be offered prenatal diagnosis.

INHERITED DEFICIENCY OF ETF DEHYDROGENASE (DH) IS A **S21 INHERITED DEFICIENCY OF BIF DEBIDANCEMBER (DI) 16 A CAUSE OF GLUTARIC ACIDEMIA TYPE II (GA2) AND ETHYLMALONIC-ADIPIC ACIDEMIA (EMA) Frank E. Freman and Stephen I. Goodman, Medical College of Wisconsin, Milwaukee, and University of Colorado School of Medicine, Denver.

GA2 is an inborn error characterized by nonketotic hypoglyce-mia, metabolic acidosis and accumulation of substrates of flavoprotein dehydrogenases that transfer electrons to the respiratory chain via ETF and ETF DH. EMA is a mild form of GA2, with a later onset and a more attenuated course.

We have previously shown absence of immunoreactive ETF DH in fibroblasts from some GA2 patients, and partial deficiency of ETF in others. We have extended these results using a catalytic assay for ETF DH, measuring comproportionation of fully reduced and oxidized ETF to ETF semiquinone; activity in 8 control fibroblast lines was 16±3 mU/mg protein. Four GA2 lines deficient in immunoreactive ETF DH had undetected activity (<0.1 mU/mg), and 2 with decreased immunoreactive ETF but apparently normal patients had activities of 12 and 13. Lines from parents of 2 ETF DH⁻ patients had activities of 8,6,4, and 5, i.e. intermediate between control and GA2 values. Four mild GA2/EMA lines were examined, showing activities of 0.7,2,3, and 7. All severely ETF DH⁻ patients had congenital anomalies, at least renal cysts ±

or degree of the block in electron transport.

We conclude: (a) ETF DH deficiency is the primary defect in some GA2 and (probably) EMA patients; (b) it is inherited as an autosomal recessive trait. The condition is a model of disordered morphogenesis caused by deficiency of a single known protein.

PARTIAL TRISOMY 11q SYNDROME: ASSOCIATION WITH MICRO-PENIS. Lytt I. Gardner, Lawrence P. Gordon, Navnit S.

PENIS. Lytt I. Gardner, Lawrence P. Gordon, Navnit S. Mitter, Douglas P. Kalinowski, Karen J. Sanders, David A. Clark and Michael H. Ratner. SUNY Upstate Medical Center, Depts. of Pediatrics, Pathology and Surgery., Syracuse. This 3 mos old boy was found to have a karyotype of 46,XY,-18, +t(11;18)(q23;q23). His mother had a balanced reciprocal translocation 46,XX,t(11;18)(23;23). He had dysmorphic, low-set ears, asymmetrical facies, epicanthus and high-arched palate. Lips had a "fish-mouth" appearance. There were: widely-spaced nipples, narrow chest,umbilical and bilateral inguinal hernias, micropenis, normal scrotum and generalized hypotonia. Autonsy at age penis, normal scrotum and generalized hypotonia. Autopsy at age

penis, normal scrotum and generalized hypotonia. Autopsy at age 13 mos showed trigonocephaly, VSD, pulmonary a. stenosis and other cardiac anomalies, and histologically normal testes in canals. Clavicles and other bones were normal by x-ray.

There have been 4 males previously described with micropenis and partial trisomy llq syndrome (Pihko et al. Hum Genet 58:129, 1981). Excluded are trisomies due to t(11;22) which may be a separate syndrome (DeFrance et al. Clin Genet 25:295, 1984). Only one other case has been reported with t(11;18), but the receptor region was 18p rather than 18q, and the 11q breakpoint was much more proximal (q14). Etiology of micropenis in partial trisomy 11q syndrome may be associated with defects in midline brain structures, e.g. corpus callosum (cf. micropenis in septo-optic dysplasia syndrome where septum pellucidum is absent). This study supports the hypothesis that most signs of partial trisomy 11q syndrome are caused by trisomy of regions distal to 11q23.