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PKU GENE - POSSIBLE CAUSE OF NON-SPECIFIC MENTAL RETARDATION. Atsuko Fujimoto and Samuel P. Bessman, USC Med. Sch., Dept. Pediatrics, Los Angeles

The Justification Hypothesis (J. Ped. 81:834, 1972) proposes that deficiencies in non-essential amino acids might cause mental retardation. The mother heterozygous for synthesis of any one of the non-essential amino acids would deprive her fetus partially and the heterozygous or homozygous fetus would be more or less unable to make up for the deficiency. Berman and Ford (Lancet i: 767, 1977) showed that such concatenation of heterozygous mother and heterozygous fetus is associated with significantly lower IQ. Our own work has verified this finding. The possibility that heterozygosity for PKU in mother and fetus might be a cause of a large amount of "non-specific" mental retardation was tested by looking for associated heterozygosity for PKU in mother and child among 12 families in a genetic clinic. Although there is no evidence of PKU in any of these families three showed such association. This is more than 10 times chance and suggests that a major factor in non-specific mental retardation is indeed heterozygosity in mother and fetus, depriving the developing fetus of a normal supply of tyrosine.

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DOMINANT INHERITANCE OF ISOLATED GROWTH HORMONE DEFICIENCY (IGHD) TRANSMITTED THROUGH AN INDIVIDUAL OF NORMAL STATURE. J.M.Gertner, M.Genel, K. Arulanantham and J.D.Crawford, Depts. of Pediat.: Yale Univ. Sch. of Med. and Yale-New Haven Hosp.;Newington (CT) Children's Hosp.; and Harvard Med.Sch. and Mass. Gen. Hosp., Boston.

Recessive and dominant inheritance of IGHD are associated with distinct phenotypes. Type I is more common, autosomal recessive, growth hormone (GH) responsive, and insulin sensitive with typical facies. Type II is autosomal dominant and insulin and GH resistant. Dominant father-child inheritance of a type I phenotype has, however, been suggested in three families, all with very short fathers.

Two pairs of brothers, first cousins, presented with IGHD in early childhood. The mother of one pair (KG height 147 cm) and her brother (RT height 176 cm), the father of the others, showed absent or grossly subnormal GH responses to L-Dopa and insulin hypoglycemia. Pituitary function was otherwise normal. Neither marriage was consanguinous and the spouses of KG and RT were unrelated. All 4 cousins responded remarkably well to GH therapy.

This pedigree is most consistent with dominant inheritance of IGHD type I in which variable expressivity is manifest by the normal stature of RT. The existence of autosomal dominant transmission of IGHD through individuals of normal stature may have implications for genetic counselling in familial short stature.

Supported by Grant RR-125, GCRC Branch, NIH.

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TREATMENT OF CYSTINOSIS WITH CYSTEAMINE. Eric P. Girardin, Margaret S. DeWolfe, John F.S. Crocker. Dalhousie University and The Izaak Walton Killam Hospital for Children, Department of Pediatrics, Halifax, N.S., Canada.

Attempts at reduction of intracellular cystine in infantile cystinosis, has been reported previously in 3 patients using dithiothreitol (2 patients) or cysteamine (mercaptoethylamine) (1 patient). We evaluated the benefit of a combination of ascorbic acid and cysteamine in a 14-month-old boy with Fanconi's syndrome and cystinosis.

The patient's granulocytes contained 5.2 - 13 nmol of cystine/mg of protein (normal $<$0.1 nmol/mg protein) and cystine crystals were present in the bone marrow. Creatinine clearance (C_{Cr}) was 13 ml/min/1.73 m^2 pre-treatment. Ascorbic acid was given as a calcium salt in a dose of 2 mg/kg/day. Cysteamine was given at 99 mg/kg/day. Within 30 days, the buffy coat cystine content had fallen to normal. The dose of cysteamine was then decreased to 30 mg/kg/day. Concurrent with the fall in leukocyte cystine content, the C_{Cr} rose to 32.8 and 50 ml/min/1.73 m^2 serially and growth improved, though these changes probably reflected other elements of treatment. No side effects were noted.

This is the first report of early treatment of cystinosis with cysteamine. Although the long-term benefit of this treatment will not be known for several years, the early satisfactory biochemical response emphasizes the need to evaluate cysteamine in other patients with cystinosis, before the disease is far advanced.

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RARE PHENOTYPES OF PLACENTAL ALKALINE PHOSPHATASE: AN ANALYSIS OF RELATIONSHIPS WITH SOME NEONATAL AND MATERNAL VARIABLES. F. Gloria-Bottini, A. Polzonetti, R. Bentivoglia, P. Lucarelli and E. Bottini (Spon. by C.D. Cook). Univ. of Camerino, Dept. of Genetics and Computer Center and Univ. of Rome, Dept. of Pediatrics.

The large number (>15) and frequency (~2%) of rare placental alkaline phosphatase (Pl) alleles represent a very special case among polymorphic enzymes. Since the Pl gene is active only during intrauterine life, the allelic diversity and its maintenance may be connected with intrauterine environment and with fetal development. 1700 newborn infants (1271 Caucasians, 337 Negroes and 92 Puerto Ricans), collected at Yale-New Haven Hospital from 1968-1971, were studied. An analysis of the relationship between rare Pl phenotype and the following 14 variables was carried out: gestational age, birth weight, maternal age, gestational order, sex, fetal and maternal ABO and Rh phenotype, feto-maternal ABO and Rh compatibility, fetal phosphoglucomutase 1 and 3 phenotype, and previous spontaneous abortions. A negative association between rare Pl phenotype and maternal O phenotype ($p<0.05$) was observed in all ethnic groups. The incidence of rare Pl types appeared to increase in the births following the first one and to decrease in those of higher order.

(Supported by NATO Grant 554).

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DRAMATIC CLINICAL RESPONSE TO COFACTOR THERAPY IN ADVANCED METHYLMALONIC ACIDEMIA (MMA). [1]Gregory A. Grabowski, [1]Francis S. Wright and [2]Robert J. Desnick. [1]Dept. of Pediatrics, University of Minnesota Hospitals, Minneapolis, and [2]Mt. Sinai School of Medicine, Division of Medical Genetics, New York.

B_{12}-responsive MMA results from inherited defects in the synthesis of 5'-deoxyadenosyl-cobalamin(*cbl*), the cofactor required for Methylmalonyl-CoA-mutase (MMM) activity. Homozygotes with these enzyme defects manifest systemic acidosis, failure to thrive, mental retardation, severe hypotonia and death in childhood. The diagnosis of MMA in a $3\frac{1}{2}$ yr. old, acidotic, retarded girl was confirmed by the findings of massive amounts of urinary methylmalonic acid (mma) and deficient MMM activity in cultured fibroblasts. Somatic cell hybridization studies with other *cbl* mutants revealed her defect to be in the *cbl a* complementation group. Dramatic biochemical and clinical responses were observed following protein restriction(P-R) and B_{12} supplementation ($B_{12}S$). mma was 30-75 g/gCr. prior to treatment; P-R (1.5g/kg/day)+ mma to 12g/gCr. by day 8. $B_{12}S$ (1 mg IM/day)+ mma to 1.5g/gCr. on day 9 and 0.23 g/gCr. by day 14. A trial of 3 g protein/kg/day + mma 10 fold. Subsequently, $B_{12}S$ (10mg p.o./day) and P-R + and maintained mma <1.0g/gCr. for the last 12 mos. Reversal of her growth, neurologic and intellectual deficits has been documented; bone age + from $1\frac{1}{2}$ to $3\frac{1}{2}$ yrs., + hypotonia, normalization of EEG, + motor skills and I.Q. + from 66 to 100. These findings support the efficacy of $B_{12}S$ and P-R therapy in untreated advanced MMA.

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AN APPARENT CHANGE IN MUTATION RATES FOR INTERCHANGE TRISOMY 21 IN LIVEBIRTHS. Ernest B. Hook, Birth Defects Institute, N.Y.S. Department of Health and Albany Medical College, Department of Pediatrics, Albany.

Down's syndrome may result either from 47,trisomy 21 or from an interchange (Robertsonian) translocation. The mutation rate for de novo interchange trisomic may be estimated from the literature indirectly as about $1.0\text{-}2.7 \times 10^{-5}$ per gamete per generation, resulting in an estimated frequency in livebirths ($2\text{-}5 \times 10^{-5}$) about 20-50 times lower than that of 47,+21 ($\sim 1 \times 10^{-3}$). Changes in the frequency of de novo interchange trisomies are difficult to investigate directly because of the large population base required. (In 50,000 consecutive newborns studied cytogenetically only one mutant case has been detected.) In contrast, the ratio of de novo interchange trisomy to 47, trisomy provides a readily available indirect index for the former event (Genetics 83: s33, 1976). This ratio is best considered by limiting analysis to younger mothers because the two cytogenetic outcomes differ markedly in their relative change in frequency with advancing maternal age. In data from New York State chromosome registry the ratio of de novo interchange trisomy 21, to 47,trisomy 21 in mothers under 30 was about .04 prior to 1973. In 1973-1975 this ratio rose to .12, consistent with a 2-3 fold increase. No direct estimates of the mutation rate from earlier years are possible but for 1975 the mutation rate in the state was about 3×10^{-5} per gamete per generation, (6×10^{-5} in livebirths) based on the number of reported cases, the number of livebirths in the state, and an estimate of completeness of the registry for all Down syndrome instances.