535 RING CHROMOSOME 12 SYNDROME

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Advances in the development of banding techniques have facilitated the identification of a number of new chromosomal abnormalities. We studied a 13 mo. old girl with a history of failure to thrive, developmental delay and dysmorphic features. Chromosomal analysis revealed ringed chromosome 12. J.T. was the product of an uncomplicated second pregnancy of a 24 yr. old woman. Birth weight and height were close to the 3rd percentile. At 13 mos. her weight age was 1 mo., height age was 3 mos. and head circumference was at 3rd percentile for 3 mos. She had epicanthal folds, mildly cupped low set ears, high arched palate, short neck with low set hairline. Total hand length was that of a 1.5 mo. old and clinodactyly and single crease of left 5th finger. Developmentally she functioned between 5-8 mos. The chromosome number was 46 in all cells and trypsin banding showed a ring 12 chromosome. Twelve percent of cells showed variable chromosome loss and 4 showed gaps or breaks in chromatids. The purpose of this report is to delineate the clinical findings and natural history of ring chromosome 12 syndrome. There are only two known cases of this syndrome with which we compared our findings. It appears that the amount of genetic material deleted from chromosome 12 determines the degree of physical abnormalities and developmental delay. The relatively high rate of the loss of the ring 12 points out the fragility of the ring chromosome.

536 EVIDENCE FOR AUTOSOMAL RECESSIVE INHERITANCE OF MITOCHONDRIAL CARBAMYL PHOSPHATE SYNTHETASE DEFICIENCY.

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Inherited deficiency of hepatic mitochondrial carbamyl phosphate synthetase (CPS I), the first enzyme of the urea cycle, is a rare cause of hyperammonemia and protein intolerance. The paucity of affected individuals and the lack of family studies have hitherto precluded definition of the mode of inheritance. We now report in its entirety a family with two children affected with partial CPS I deficiency. The proband, a 16 year old girl, was ascertained when hyperammonemia accompanied an episode of encephalopathy. Moderate psychomotor retardation in the proband and her two sibs (1 female; 1 male) necessitated diagnostic liver biopsies for urea cycle enzyme assays. Isolated deficiency of CPS I was observed in the proband's liver (6% of control mean) and that of her sister (5% of control); the brother's activity was well within the range of appropriate control values (see table).

Subject	CPS I activity (μmol/hr/mg)
Proband	0.18
Female Sib	0.16
Male Sib	2.35
Father	0.95
Mother	1.57
Controls(n=8)	2.98±0.58($\bar{x}$±1SD) 2.01-3.74(range)

Significantly, CPS I activity in the liver of both unrelated parents fell between the deficient values in the affected girls and the normal range. These results suggest strongly that CPS I deficiency is inherited as an autosomal recessive trait.

537 HYPOPHOSPHATASIA (A FAMILY STUDY) AND TURNER SYNDROME

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A patient with Turner Syndrome (TS) (45,XO) diagnosed by age 2 years had at age 5 years, rachitic changes on chest x-ray, a healing traumatic fracture of the left femur and metaphyseal changes consistent with hypophosphatasia (H). The diagnosis was confirmed by a low serum alkaline phosphatase (AP) (125 mu/ml) in the presence of a fracture, elevated urinary excretion of phosphoethanolamine (PEA) (33.6 mg/day) and early shedding of deciduous teeth. Malabsorption, glomerular and tubular renal diseases were excluded by appropriate investigations. Because of limited growth potential in TS and further impairment by the concommitent occurence of H, a trial of phosphate therapy was felt to be indicated. A bone biopsy after tetracycline labelling was performed prior to the initiation of therapy; biopsy will be repeated after 6 months of therapy (1/78). The clinical response to therapy suggests a nearly twofold increase in growth rate.

Historically and radiologically the paternal side was free of disease; 4/7 in the mother's sibship showed radiographic evidence of bone dysplasia in childhood. Total AP was low in the mother and her affected sister, and normal in the father. PEA excretion studies and AP isoenzyme determinations are in progress

This is the first report of the simultaneous occurrence of TS and H. The family study suggests that the H is transmitted as an autosomal dominant trait.

538 ETHYLMALONIC-ADIPIC ACIDURIA: A NEW DEFECT OF BUTYRATE OXIDATION ASSOCIATED WITH HYPOGLYCEMIA.

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A 5 year old girl with recurrent hypoglycemia, acidosis and normal development was found to excrete in her urine massive quantities of ethylmalonic acid (EMA), adipic acid (AA) and hexonylglycine (HG): 670-780, 210-740 and 190-390 μg/mg creatinine, respectively, vs. normal values of <9 μg/mg for each. Since butyryl CoA can be carboxylated to form EMA, and hexanoyl CoA can be either ω-oxidized to AA or conjugated with glycine to form HG, this pattern of urinary metabolites suggested a deficiency of butyryl CoA dehydrogenase, a mitochondrial enzyme oxidizing both butyryl and hexanoyl CoA. Such a deficiency was supported by a medium chain triglyceride challenge which markedly augmented EMA excretion, and by studies on oxidation of [1-^{14}C]butyrate by cultured skin fibroblasts which revealed $^{14}CO_2$ production by patient's cells consistently <15% of that in 6 control lines.

The urinary findings in our patient resemble those seen in Jamaican vomiting sickness and glutaric aciduria type II, both characterized by defects of multiple acyl CoA dehydrogenases. The cultured cell findings noted above, however, the excretion of only minimal amounts of glutarate and the results of oral lysine and leucine loading tests make these diagnoses most unlikely. We suggest that our patient suffers from an inheritent isolated deficiency of butyryl CoA dehydrogenase. The hypoglycemia may be explained by accumulation of EMA, which has been shown to inhibit mitochondrial malate transport, a rate limiting step in gluconeogenesis.

539 PRESUMPTIVE EVIDENCE FOR THE PRESENCE OF 2 ACTIVE X CHROMOSOMES IN A BALANCED X-AUTOSOMAL TRANSLOCATION.

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In human somatic cells, X chromosomes in excess of one are late replicating. In balanced X-autosome translocation, the general rule is that the normal X is late replicating. We are reporting the first such translocation in which there is no late replicating X in 1/3 of cells analyzed. A 6-year-old girl with the Beckwith-Wiedemann syndrome has a balanced, de novo, X;1 translocation (G-banded karyotype is 46,X,t(X;1) (Xpter→Xq26::1q12→1qter; 1pter→1q12::Xq26→Xqter). Using the BrdU terminal pulse method followed by acridine orange or Hoechst 33258 stain and giemsa in 2 successive lymphocyte cultures, the normal X was identified as late replicating in approximately 66% of metaphases. In the remaining 34% of cells, neither the normal X nor the Xt appeared to be late replicating. In these cells, regions of chromosomes 4 and 13, known to be late replicating, are clearly identifiable. In no case did the small Xq portion in the reciprocal translocation chromosome appear as late replicating. This finding serves as presumptive evidence for the presence of 2 active X chromosomes in a balanced X-autosome translocation.

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540 KERATAN AND HEPARAN SULFATURIA - A NEW MUCOPOLYSACCHARIDOSIS WITH N-ACETYLGLUCOSAMINE 6- SULFATASE DEFICIENCY.

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A 3½-year old child with severe skeletal dysplasia similar to Morquio syndrome, but with mental retardation had increased urinary mucopolysaccharides with unusual composition of 20% heparan sulfate and 75% keratan sulfate. Extracts of cultured skin fibroblasts from the patient contained normal levels of aryl sulfatases A, B and C, β-N-acetylhexosaminidase and β-galactosidase. Fibroblast extracts were incubated with (^{35}S) N-acetylgalactosamine 6-sulfate as substrate and were found to have normal activity of the enzyme hydrolyzing this substrate. This finding is in contrast to Morquio syndrome where a deficiency of this enzyme is characteristic. A disaccharide containing (^{35}S) N-acetylglucosamine 6-sulfate was prepared from chick embryo keratan sulfate. A profound deficiency in the hydrolysis of $^{35}SO_4$ (1%) from this substrate was observed, while extracts of Morquio and normal fibroblasts readily hydrolyze (25%) $^{35}SO_4$ from this substrate. On the basis of these data a new mucopolysaccharidosis, distinct from Morquio syndrome, with a different sulfatase deficiency (N-acetylglucosamine 6-sulfatase) is described. The deficiency in Morquio syndrome is that of N-acetylgalactosamine and galactose 6-sulfatase. DiFerrante et al. (Science, in press) have reported similar findings in another patient. Supported by Nat'l Foundation Grant 244-39-66-321.