

- **865** PARENTAL PRECONCEPTIONAL IONIZING RADIATION AND ANEUPLOID CHILDREN. Philip L. Townes and Elissa M. Kraus. Univ. of Mass. Med. Center, Dept. of Pediatrics, Worcester.

Parental preconceptional (lifetime) radiation histories were routinely obtained during intake interviews of consultands to Genetic Clinic at Univ. of Rochester Med. Center and Univ. of Mass. Med. Center. The data were recorded in a standardized format prior to our clinical and cytogenetic evaluation of the patients. Gonadal exposures for the parents of 300 randomly selected aneuploid patients and 300 concurrently ascertained control patients with normal chromosome complements have been calculated from standard tables. The aneuploid group consisted of 210 patients with Down syndrome, 35 with other major autosomal abnormalities, and 55 sex chromosome abnormalities. In control group, mean maternal gonadal radiation equals 157.95 mrad; paternal 48.62 mrad. In Down syndrome group, mean maternal gonadal radiation equals 258.79 mrad; paternal 98.71 mrad. In other autosomal abnormalities, maternal equals 180.72 mrad; paternal 43.18 mrad. In sex chromosome abnormalities, maternal equals 144.72 mrad; paternal 61.85 mrad. Of interest is marked increase in both maternal and paternal exposure of parents of children with Down syndrome. This difference is not entirely explained by advanced parental age in this group. Mean maternal age of controls equals 26.4 years; paternal equals 28.9 years. Mean maternal age of parents with Down syndrome children equals 29.5 years; mean paternal age equals 31.9 years. These observations support notion that parental x-ray exposure may be a significant factor in the etiology of Down syndrome.

- △ **866** DNA MARKERS ASSOCIATED WITH HUMAN PROCOLLAGEN GENES. P. Tsipouras^{1,2}, M.-L. Chu¹, F.O. Sangiorgi¹, D. Weil¹, and F. Ramirez^{1,3}. Departments of ¹Biochemistry, ²Pediatrics and ³Obstetrics-Gynecology, UMDNJ-Rutgers Medical School, Piscataway, New Jersey

Four loci dispersed on different chromosomes are coding for the proc chains of the 3 types of fibrillar collagen in human. Structural mutations of these genes have been demonstrated in osteogenesis imperfecta (OI), Ehlers-Danlos S. types IV and VII (EDS), Marfan S. and certain chondrodystrophies. DNA markers (RFLP) have been identified and used for genetic linkage studies in some of these disorders. In the *pro α 2(I)* gene, 3 RFLP's generated by the EcoRI, MspI and StuI restriction endonucleases (RE) have been utilized for linkage studies in 15 families with an autosomal dominant form of OI. With the use of the molecular haplotypes we established linkage in 3 families, ruled out linkage in 5 while the remaining 7 were not informative. The 3 families with the specific *pro α 2(I)* collagen gene association belong to a distinct phenotypic group (OI type IV). Biochemical studies revealed that the defect in an affected individual is a small deletion in the middle of the *pro α 2(I)* chain. Similarly, 2 high frequency DNA polymorphisms, generated by the Hind III and EcoRI RE, associated with the *pro α 1(II)* gene and 4 RFLP's generated by the Hind III, EcoRI, MspI and XhoI RE, and associated with the *pro α 1(III)* gene have been identified. Preliminary data on linkage studies utilizing the *pro α 1(III)* RFLP's emphasized the informative power of these markers in defining the molecular heterogeneity of EDS IV.

- **867** SELECTIVE TRANSMISSION OF INSULIN DEPENDENT DIABETES GENES? CM Vadheim, JJ Rotter, NK Maclaren, WJ Riley, CE Anderson, Medical Genetics, Harbor-UCLA, Torrance, CA; University of Florida, Gainesville.

A major unresolved puzzle in IDDM genetics is the high frequency of this previously fatal disorder. One possible selective advantage would be differential transmission of diabetes predisposing genes. If so, we would predict that HLA alleles DR3 and DR4 will be preferentially transmitted to offspring compared to other alleles. In addition, if this mechanism operates via in utero selection, then certain HLA mating types may be more common among parents with a history of spontaneous abortion (SAB). We tested these hypotheses in 107 families ascertained through a child with IDDM. Affected and unaffected offspring inherited a parents' DR3 allele significantly more often than expected (67% vs 50%; $p < .001$). In addition, both affected and unaffected offspring inherited a father's DR4 allele significantly more often than a mother's DR4 allele (72.1% vs 55.6%; $p < .005$), providing an explanation for the recent observation that risk for IDDM is higher in offspring of male IDDMs. In support of the hypothesis that distorted transmission is mediated by in utero selection, we observed that IDDM couples with SABs had a DR4 father and DR3 haplotype mother significantly more often than did non-SAB IDDM couples (71.4% vs 21.8%; $p < .001$). Thus our data provide evidence for preferential in utero survival and transmission of HLA alleles that predispose to IDDM, and in addition provide a potential mechanism for the maintenance of the high population frequency for this previously genetically lethal disease.

- **868** A PRACTICAL METAPHASE MARKER OF THE INACTIVE X CHROMOSOME. Daniel L. Van Dyke, Wendy L. Flejter, Maria J. Worsham, Jacquelyn R. Roberson, Lester Weiss. Henry Ford Hospital, Medical Genetics and Birth Defects Center, Detroit, MI.

The ability to identify the inactivated X chromosome with routine G- or Q-banding would have broad clinical and research applicability. We recently reported that the inactivated X frequently bands or folds in region Xq13Xq21 (Flejter et al, Am J Hum Genet 36:218, 1984). The fold occurs in about 88% of prometaphase, 50% of early metaphase, 30% of midmetaphase, and 10% of late metaphase inactive X's. In prometaphase, the site of folding includes Xq11.2 and Xq13.3, infrequently extending to Xq21.1. An omega-shaped loop is frequently formed between sub-bands Xq11.2 and Xq13.3. It is paradoxical that the inactive X is the only chromosome identifiable in interphase, yet in metaphase it cannot be distinguished from its active homolog. The specific inactivation-associated fold at region Xq1 resolves that paradox and is a useful marker of the inactive X. 1. The KOP translocation, t(X;14)(q13;q32), has nearly all of Xq translocated to 14q (Allerdice et al, Am J Med Genet 2:223, 1978). Cell line GM0074 has one normal 14, one Xq, two der(14) chromosomes, and a Y. One der(14) folded in 10/18 cells scored, confirming translocation of the inactivation center adjacent to 14q distal. 2. Metaphase cells from other primates had a specific fold in the same region as in the human X: at Xq13-Xq21 in 2 gorillas, 1 chimp, 2 pygmy chimps, 1 orang, 1 baboon, 1 rhesus and 1 stump-tail monkey. This is further evidence for evolutionary conservation of the X chromosome. One chimpanzee exhibited the fold at Xq24; we suspect a pericentric inv in this individual. We have not seen a frequent fold in the X of a bat (*Isardira brasiliensis*), chinese hamster (*Cricetulus griseus*), or rat kangaroo (*Potorous tridactylus*). 3. Regarding the relationship of X inactivation and intelligence in fra(X)(q28) carriers, we observe that in cells of normal carriers the fold was mostly on the fragile X-positive chromosome, whereas in cells of an affected carrier the fold was mostly on the fragile X-negative chromosome. This is evidence that inactivation of the fragile X chromosome is positively correlated with intelligence in carriers.

- 869** FIVE YEAR FOLLOW-UP OF CREATINE SUPPLEMENTATION IN GYRATE ATROPHY OF THE CHOROID AND RETINA (GA). Kaarina Vannas-Sulonen, Ilkka Sipilä, Antti Vannas, Juhani Rapola and Olli Simell (Spon. by David Rosenblatt). Department of Ophthalmology and Children's Hospital, University of Helsinki, Helsinki, Finland.

GA is an autosomal recessive disorder with characteristic chorioretinal degeneration; atrophy and tubular aggregates in type II muscle fibers; 10-20 fold increase in ornithine concentration in body fluids; and deficient activity of ornithine- δ -aminotransferase. Based on the inhibition by high ornithine concentration of the rate-limiting enzyme of creatine synthesis, the low excretion of the reaction product (guanidinoacetic acid), and low serum and urinary concentrations of creatine and creatinine in the patients, creatine and creatine phosphate deficiency has been suggested to be involved in the pathogenesis of GA. We supplemented 13 patients (age 6-31 years) with creatine, 0.5 g x 3 daily for 36-72 months. Deterioration of visual function tests and fundus photographs was seen during the treatment, apparently with similar velocity as in untreated cases. Deterioration varied considerably among individuals, being fastest in the youngest patients. Muscle abnormalities decreased or disappeared within months of the initiation of the therapy; changes reappeared in two who discontinued supplementation. Differences in creatine responses in the two organs may depend on too small creatine dosage, impermeability of blood-eye barrier for creatine, or on different mechanisms of the atrophy in muscle and eye.

- 870** TWO APPARENTLY BALANCED DE NOVO RECIPROCAL TRANSLOCATIONS IN A GIRL WITH GLOBAL DEVELOPMENTAL DELAY AND MILD DYSMORPHISM.

Jannell Welsh-Sloan, Navnit S. Mitter, Lytt L. Gardner and James Coplan, SUNY Upstate Medical Center, Depts. of Pediatrics and Pathology, Syracuse.

The patient was born at 35 wks gestation, following a pregnancy remarkable only for some first trimester spotting. Her birth wt was 1.87 Kg. She first rolled over at 9 mos, stood alone at 21 mos. and walked at 22 mos. At age 4 yrs the patient was seen for evaluation of severely delayed speech and global developmental delay. She presented as a small child with height and weight both below the 3rd %ile and head circumference at the 40th %ile. She had an aberrant occipital hair whorl, epicanthal folds, flat nasal bridge and small nasal tip. Analysis of GTG-banded, cultured peripheral lymphocytes revealed a karyotype of 46,X,t(X;3)(q26;q29),t(8;11)(q11.2;p11.2). The parents were found to have normal chromosomes, suggesting *de novo* origin of both apparently balanced reciprocal translocations in the patient, an extremely rare event. Random facultative heterochromatization of chromosome X may explain the presence of mild dysmorphism and global developmental delay. She could be displaying the effects of a functional partial 3q monosomy due to the extension of facultative heterochromatization to the autosome.