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IN SITU HYBRIDIZATION AND TRANSLOCATION BREAKPOINT MAPPING III. DIGEORGE SYNDROME (DGS) WITH PARTIAL MONOSOMY OF CHROMOSOME 22. Linda A. Cannizzaro, Beverly S. Emanuel (Spon. by Roger L. Ladda). Penn State Univ. Coll. of Med., The M. S. Hershey Med. Ctr., Dept. of Peds., Hershey, PA and Univ. of PA, Children's Hosp. of Phila., Phila.

DiGeorge Syndrome is characterized by a spectrum of congenital malformations. Studies have shown an association between DGS and deletion of chromosome 22 resulting in the loss of 22pter→q11 and translocation of its distal long arm (22q11→qter) to one of several autosomes (3q, 4q, 10q, 20q). Two cell lines were used for this study. The first, from a balanced translocation carrier, the father of a patient with DGS, has a karyotype of 46, XY, t(10;22)(q25,q11). The der 22 extending from 22pter to q11 is retained. The second cell line, established from a DGS patient, has a karyotype of 45, XY, -4, -22, + der (4), t(4;22)(q35.2;q11.2). This line is monosomic for the region 22pter to q11 and for the region 4q35.2 to qter. "In situ" hybridization with a constant region probe for the immunoglobulin light chain gene cluster (IGLC) reveals strong hybridization to the normal 22 in the q11 region and to the other involved translocation chromosome, 10q+ or 4q+. No hybridization was observed to the der 22 of the balanced carrier. These results suggest that all of the IGLC constant region from chromosome 22 is translocated to the relevant autosomes involved in these DGS related rearrangements and the breakpoint for each rearrangement is proximal to the c-lambda locus in 22q11. It is possible that the breakpoint for DGS lies within the variable region since v-lambda is proximal to c-lambda in 22q11.

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TRANSLOCATION BREAKPOINT MAPPING OF 9;22 ALL AND 8;22 BURKITT'S LYMPHOMA REVEALS DIFFERING BREAKPOINTS WITHIN 22q11. Linda A. Cannizzaro, Peter C. Nowell, Jan Erikson, Carlo M. Croce, Beverly S. Emanuel. (Spon. by Roger L. Ladda). Penn State Univ. Coll. of Med., The M. S. Hershey Med. Ctr., Dept. of Peds, Hershey, PA, Univ. of PA, Children's Hosp. of Phila., Depts. of Path. and Human Genetics, Phila., PA, and The Wistar Institute, Phila. PA.

In situ hybridization and Southern blot analysis were performed on bone marrow from a child with Ph' positive 9;22 ALL and on PA 682, a cell line from a patient with 8;22 Burkitt's lymphoma (BL). We used a cDNA probe from the constant region of the immunoglobulin light chain gene complex (IGLC) to examine the translocation breakpoint in 22q11. In PA 682, the results of four "in situ" experiments with c-lambda reveal hybridization to the 8q+ and the normal 22 and no hybridization to the 22q-. These results suggest that in 8;22 BL, all of c-lambda of IGLC is translocated onto the 8q+ chromosome and the translocation breakpoint is proximal to c-lambda. We also performed two "in situ" experiments with the c-lambda probe on direct marrow preparations from a child with Ph' positive 9;22 ALL. In each experiment c-lambda is hybridized to the normal 22 and to the 22q- as well as to the 9q+. The levels of c-lambda hybridization to the 9q+, between 6-7.3% of the total grains, were significantly higher than background levels. These results suggest that the translocation breakpoint of 9;22 ALL interrupts the constant region cluster of IGLC and is distal to the 22q11 breakpoint of 8;22 BL.

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CEREBELLAR AGENESIS AND HEMIFACIAL MICROSOPIA IN AN INFANT WITH 22q PARTIAL TRISOMY SYNDROME. David Chitayat, Nava Furman, Boaz Milbauer and Cyril Legum. Departments of Pediatrics, Genetics and Neonatology, Tel-Aviv Medical Center and Sackler School of Medicine, Tel-Aviv, Israel.

Partial 22q trisomy syndrome has been well documented with the frequently occurring features of growth retardation, hypertelorism, coloboma of iris (Cat's eye), preauricular skin tags and sinuses, dysplastic low set ears, congenital heart disease, anal atresia, renal anomalies, agenesis of corpus callosum and of cerebellar vermis, mental retardation and hypotonia or hypertonia.

We report an infant with a karyotype of 47XY + del (22)(q12) born to a mother with 46, XX, t(11;22)(q23;q12) with two additional features: cerebellar agenesis and hemifacial microsomia. The latter features have not been described previously in partial 22q trisomy.

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PSEUDOHYPOALDOSTERONISM IN A FEMALE INFANT AND HER FAMILY: DIVERSITY OF CLINICAL EXPRESSION AND MODE OF INHERITANCE. David Chitayat, Zvi Spier, Dan Ayalon and Avi Golaner. Department of Paediatrics and Tinsit Institute of Reproductive Endocrinology, Tel-Aviv Medical Center and the Sackler School of Medicine, Tel-Aviv University, Israel.

Pseudohypoaldosteronism (PHA) was diagnosed in an infant who clinically presented with severe failure to thrive (FTT) and vomiting. There were no abnormal physical findings. The serum chemistry (mmol/L) were: Na-129, K-7.6; Co₂-18; Cl-105; Urea 10. 17 (OH) progesterone was normal, serum aldosterone 207ng/dl (normal range 2-20ng/dl), plasma renin was greater than 13.6ng/ml/h (normal range 0.5-1.9ng/ml/h) in supine position. These results were consistent with the diagnosis of PHA. Evaluation of her extended family revealed that her mother and one maternal sibling had probable transient symptomatic PHA in infancy (presented as FTT vomiting and dehydration) and now have asymptomatic hyperaldosteronism; 4 more maternal siblings died with the same manifestations, and the patient's sister and a maternal uncle and aunt have asymptomatic PHA. The mode of inheritance in this family is consistent with an autosomal dominant disorder. Salt supplementation during infancy was effective in restoring normal growth, weight gain and serum electrolytes, but not aldosterone plasma levels. It is possible that PHA in its asymptomatic form is much more common than recognized and should be considered in the work up of infants with FTT. Current evidence suggests that this disorder is due to renal tubular unresponsiveness to aldosterone.

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GM3 GANGLIOSIDOSIS: RE-CLASSIFICATION AS AN X-LINKED DYSHISTOGENETIC SYNDROME OF UNKNOWN ETIOLOGY. Joe T. R. Clarke, Stephen J. Qualman, Laurence E. Becker and Gregory J. Wilson. Hospital for Sick Children, Dept. of Pediatrics, Genetics, and Pathology, Toronto, Ontario.

A male infant cousin of a patient with "GM3 gangliosidosis" was born at 29 wks gestation to Jewish parents. The infant closely resembled his cousin with coarse facies, low hairline, low-set and posteriorly rotated ears, macroglossia, gingival hypertrophy, micragnathia, cleft palate, redundant nuchal skin, umbilical and inguinal hernias, mild hepatosplenomegaly, cryptorchidism, hypotonia then spasticity and seizures. Chromosome analysis, skeletal x-rays, bone marrow smear and urinary mucopolysaccharides, oligosaccharides, organic acids and aminoacids were normal. Measurement of multiple leukocyte lysosomal hydrolases showed normal activities. The patient died at 4 mons of age. At autopsy, the brain was small (473 g) and showed patchy demyelination, reactive gliosis, and glial and neuronal heterotopias throughout the CNS. Anomalous cerebellar extension around the ventral surface of the medulla was also present. The kidneys showed diffuse glomerulocystic disease with dilatation of Bowman's capsule. Biochemical analysis of brain showed decreased levels of myelin glycolipids. However, in contrast to the cousin with "GM3 gangliosidosis", the concentration and pattern of brain gangliosides were normal. These findings, along with those reported from studies on a second, similarly affected, male cousin, indicate that the disease originally described as "GM3 gangliosidosis" should be re-classified as an X-linked dyshistogenetic syndrome of unknown etiology.

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GENETICS OF INSULIN DEPENDENT DIABETES MELLITUS (DM) IN THE RAT. Eleanor Colle, Ronald D. Guttman, Depts. of Pediatrics & Medicine, McGill University, Montreal.

We have previously reported studies of the association of gene products of the rat major histocompatibility complex (RTL) with DM in the rat. In crosses between the diabetic BB rat (RTL.A^uB^uD^u) and inbred Lewis (RTL.A^lB^lD^l) or Buffalo (RTL.A^uB^uD^u) rats, the presence of at least 1 u haplotype is a necessary but not sufficient condition for the development of DM. We have further reported that the Class II gene products (RTL.B and RTL.D) of the RTL u haplotypes from DM rats do not differ from those of the inbred Wistar Furth (RTL.A^uB^uD^u) rat. We now report on the segregation of diabetes in litters in which there were animals with more than one RTL genotype and more than one rat with DM. Progeny from 10 mating pairs were examined; 6 were (u/u X u/x), 3 (u/x X u/x), and 1 (u/x X x/x) where x=RTL allele other than u. 121 pups were typed at the RTL A locus. There were 23 diabetics, 12 u/x and 11 u/u. In each litter, however, all of the diabetic sibs shared the same genotype. A recombination event between the Class I A locus and the Class II B and D loci was ruled out by mixed lymphocyte cultures. The results suggest that in addition to the requirement for at least 1 u haplotype, there may be a second gene conferring susceptibility to DM which is linked to RTL.