# GENETICS

**799** ADULT GAUCHER DISEASE (TYPE 1) AND COMPOUND HETEROZYGOTE (TYPE 1 AND 2) IN A GREEK FAMILY Moris Angulo, Sujatha Kosuri, Mariano Castro-Magana, Jack Sherman, Gregory Graworsky and Platon Collipp. Nassau Cty Med Ctr, SUNY, Stony Brook Health Sci Ctr, Dept. of Ped., E. Meadow, NY 11554.

Gaucher disease (GD) is an autosomal recessive condition that presents in a variety of clinical forms, better known as adult, infantile and juvenile or Type 1, 2 and 3 GD respectively.

A 22 month old greek female presented with history of progressive difficulties in breathing and swallowing and anemia plus splenomegaly noticed at the age of 3 months. She had normal growth and development, physical exam revealed a pale child with clinical picture of "Pseudobulbar palsy", strabism, abdominal distention, hepatomegaly and massive splenomegaly. She had microcytic anemia, thrombocytopenia, increased acid phosphatase, foam cell in bone marrow aspiration and Erlenmeyer flask deformity of distal femurs. Her Hb electrophoresis, G-6-PD activity, RBC osmotic fragility ferritin, liver enzymes and chest x-ray were normal. There was a history of anemia and splenomegaly in her mother and maternal aunt. Her mother has been asymptomatic since 1981 when she underwent splenectomy. Glucosylceramide-$\beta$-glucosidase activity in leukocytes and skin fibroblasts was compatible with homozygote state in both, mother and child and heterozygote in the father. The findings in this family represents a rare compound heterozygote child with clinical manifestations of type 2 GD as result of a mating between a carrier of infantile GD and an homozygote of adult GD. Discrimination between izozymes for type 1 and 2 could have been interesting unfortunately cross reacting material to all 3 forms of the enzyme is commonly seen.

**● 800** ANALYSIS OF DNA HAPLOTYPES SUGGESTS A GENETIC PREDISPOSITION TO TRISOMY 21 ASSOCIATED WITH DNA SEQUENCES ON CHROMOSOME 21. SE Antonarakis[1], SD Kittur[1], C Metaxotou[2], AS Patel[1], PE Watkins[3]. [1]Johns Hopkins Univ. Sch. of Med., Ped. Genetics Unit, Baltimore, MD, [2]Athens Univ. Sch. of Med., Athens, Greece, [3]Integrated Genetics, Inc., Framingham, MA. (Spon. by HH Kazazian Jr.)

To test the hypothesis that there is a genetic predisposition to non-disjunction (NDJ) associated with DNA sequences on chromosome 21 (C21), we used DNA polymorphism haplotypes for C21s to examine the distribution of different C21s in Down Syndrome (DS) and control families. The C21s from 20 Greek families with DS and 27 control Greek families have been examined for haplotypes using four common polymorphic sites adjacent to two very closely linked single copy DNA sequences which map to the proximal long arm of C21. Three haplotypes ++++, +---, -+++ with frequencies of 43/108, 24/108, 23/108, respectively, account for the majority of C21s in the control families. However, in the DS families haplotype -+++ was commonly associated with C21s which underwent NDJ (frequency 21/50, $X^2 = 9.6$, p=0.023, df=3). There was no difference between the haplotypes of C21s which did not participate in NDJ in the DS families and those of the control families. In addition, DS and control families did not differ in the distribution of haplotypes for two DNA polymorphisms on chromosome 17. We conclude that the C21 which is marked in Greeks by -+++ for the four polymorphic sites examined is found much more commonly in chromosomes which participate in NDJ than in controls. We propose an increased tendency for NDJ due to DNA sequences associated with a subset of C21s bearing this haplotype.

**● 801** DIAGNOSIS AND CARRIER DETECTION OF TAY-SACHS DISEASE USING SULFATED FLUOROGENIC SUBSTRATES: DIRECT DETERMINATION OF HEXOSAMINIDASE A IN SERUM DURING PREGNANCY AND IN THE PRESENCE OF HEREDITARY HEATLABILE HEXOSAMINIDASE B Yoav Ben-Yoseph, Joanne E. Reid and Henry L. Nadler. Wayne State U., Dept. of Pediatrics and Obstetrics-Gynecology, Detroit.

4-Methylumbelliferyl derivatives of β-N-acetylglucosamine-6-sulfate and β-N-acetylgalactosamine-6-sulfate were prepared by direct sulfation of the commonly used unsulfated derivatives. Both sulfated substrates were highly specific for hexosaminidase (Hex) A and in fractionated samples more than 97% of these activities was found in the Hex A fraction. The thermolability of Hex B and intermediate forms as found in subjects with hereditary heatlabile Hex B, and the increase in an intermediate Hex form as found in serum during pregnancy (Hex P), had no effect on direct determination of Hex A with the sulfated fluorogenic substrates. Serum and leukocytes from patients with infantile Tay-Sachs disease (TSD), including a TSD patient with heatlabile Hex B, had less than 2% of the respective mean activity of non-carriers. The latter patient was estimated to have 24% Hex A based on the heat inactivation method. Carrier values in serum during pregnancy and in samples with heatlabile Hex B were within the range of other carrier values and clearly separated from the respective non-carrier values. Mean carrier activities were 51-56% of the respective non-carrier means. The values of % Hex A as derived from the ratio between activities toward sulfated and unsulfated substrates were comparable to those obtained by heat inactivation excluding those with heatlabile Hex B. This helps detecting TSD genotypes and discriminates them from Sandhoff disease genotypes.

**802** TERMINAL LONG ARM DELETION OF CHROMOSOME 1, A CLINICALLY RECOGNIZABLE SYNDROME. Nesrin Bingol, Magdalena Fuchs, Edward Gendel, Vivien Diaz (Sponsored by Edward Wasserman) New York Medical College, Metropolitan Hospital Medical Center, Department of Pediatrics, New York City.

We are reporting a one year old Hispanic female with terminal deletion of the long arm of chromosome 1 [del (1) (q43qter)], and reviewing all cases from the literature. With our patient there are 12 known (1q-) syndromes, of these seven were reported from the U.S.

All patients had severe mental retardation, growth deficiency and unusual facial features; microcephaly, sparse fine hair, eye and ear malformations, flat nasal bridge with bulbous nose, carp-like mouth with tucked-in lower lip and micrognathia. Variable associated malformations of skeletal, cardiac, and genital systems were present in most.

The typical facial dysmorphology along with the associated abnormalities makes (1q-) a clinically definable syndrome. Despite the striking similarities of the dysmorphic features in this syndrome, only three of the 12 known cases were diagnosed at birth by karyotyping. In half of the patients the physicians focused their attention on the respiratory problems occurring in the neonatal period, and the mental retardation was attributed to perinatal hypoxia. Two of the 12 cases were familial, while 10 were de novo deletions. Recognition of this syndrome is more significant in familial cases where a phenotypically normal parent with the balanced translocation may have several affected offspring necessitating genetic counseling and prenatal diagnosis

**● 803** IDENTIFICATION OF HETEROZYGOSITY FOR ORNITHINE TRANSCARBAMYLASE DEFICIENCY (OTCD). Saul W. Brusilow and David L. Valle. Johns Hopkins Univ. Sch. of Medicine, Dept. Pediatrics, Balto.,Md.

This study was designed to determine the reliability of the protein tolerance test (PTT) in establishing heterozygosity for OTCD and hence aid in prenatal counseling and fetal diagnosis by DNA analysis in monoplex families. The results of the PTT done on 14 control women was compared to those done on 7 obligate heterozygotes. The peak urinary orotic acid (UOA) (ug orotic acid per mg creatinine) in the 14 control women varied from 0.4 to 2.0 with a mean (±SEM) peak value of 1.1. ± 0.11. The peak UOA in 7 obligate heterozygotes varied from 23.1 to 324 with a mean peak value of 179 ± 39. The absence of overlap and a p value of $< .001$ suggests that the PTT may be of great help in distinguishing between carriers and non-carriers of the OTCD gene. Accordingly, nine women at risk for being heterozygous for OTCD as a consequence of having borne an affected male or a symptomatic female were also studied: three of these women had UOA in the normal range (0.7, 0.98, 1.3); five had UOA in the obligate heterozygote range (20.9 to 73.5; one UOA value was ambiguous (4.9). Although these data require amplification they suggest that approximately one-third of male or female infants affected with OTCD are the result of a new mutation in a parental germ cell and that the mothers of these children are not heterozygotes. Women with ambiguous UOA values may be confirmed as carriers if a PTT done on the maternal grandmother of the affected child is unequivocally positive.

**† 804** cDNA CLONES FOR HUMAN SPHINGOMYELINASE ISOLATED USING THE λGT 11 SYSTEM. John W.Callahan,D.Joan Davidson, Prema Shankaran, and Stuart J. Freeman. The Hospital for Sick Children,Neurosciences Division, Toronto, Canada.

Human acid sphingomyelinase activity is deficient in two variants of Niemann-Pick disease, called Types A and B. Type C variants have near normal enzyme activity. The genetic expression of each of these diseases is poorly defined. Our approach to date has been to characterize the structural and kinetic properties of human sphingomyelinase and we have recently characterized a monoclonal antibody against the protein.

Using the monoclonal antibody and a λgt 11 expression library , prepared by Drs.J.S.O'Brien and J.de Wet, with cDNA against human hepatoma mRNA, we have succeeded in isolating 6 immunopositive clones. The initial screening used $1x10^6$ recombinants per dish and immunodetection used hybridoma culture fluid (10-30 µg of monoclonal antibody/ml) and peroxidase labeled goat anti-mouse antibody. One clone produced a fusion protein of about 122,000 daltons while a second produced one of 124,000 daltons corresponding to about 6000 and 8000 daltons of sphingomyelinase protein respectively. These were detected using a anti-E.coli ß-galactosidase serum. Immunological identity with sphingomyelinase was shown by direct immunoprecipitation of the fusion protein by anti-sphingomyelinase antibody and by inhibition of immunoreaction with native enzyme. The corresponding cDNA inserts, released by $EcoR_1$ digestion, are 150 bp and 250 bp respectively. These data demonstrate the application of monoclonal antibodies to cDNA cloning and the successful isolation of cDNA clones for human sphingomyelinase.