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GENETICS AND NATURAL HISTORY OF MATURITY ONSET DIABETES OF THE YOUNG. M. Jaworski, E. Colle, R. Guttmann, M. Belmonte, Dept. Ped. & Med., McGill University, Montreal Children's Hospital, Montreal.

Families with a 3 generation of a mild autosomal dominant form of diabetes mellitus (MODY) were HLA typed at the A and B loci. In family A, 6/6 affected members shared the same haplo type (A1,B8). In family B, 4/5 affected members had haplotype A29,B7. In family C, 1/2 affected members had haplotype A1,B8. With one exception, family members who lack these particular haplotypes do not develop MODY. This indicates a possible linkage between the genes in the HLA region and the gene(s) coding for susceptibility to MODY. Several affected members in family A have been followed with serial oral glucose tolerance tests (OGTT). Suring childhood, the fasting plasma glucose is high and the glucose peak during the OGTT is elevated and delayed. Simultaneous plasma insulin levels are quantitatively normal, but inappropriately low in relation to the elevated plasma glucose. During adolescence, deterioration in the OGTT often occurs; affected individuals fail to produce the physiologic increase in insulin output expected at this age. Treatment with tolbutamide displaces the OGTT curve downwards, but does not alter its shape. These individuals may at times be placed on insulin. Since the mode of inheritance and the prognosis appear to be entirely different from that of insulin dependent juvenile onset diabetes (JOD), it is important to distinguish children with MODY from those with classical JOD when planning studies of etiology or of assessments of therapy.

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GENE FREQUENCIES FOR TAY-SACHS (TSD) AND SANDHOFF'S DISEASE (SD) IN JEWISH AND NONJEWISH POPULATIONS. Michael Kaback, Phyllis Hirsch, Chitra Roy, Susan Greenwald, & Michael Kirk. UCLA-Harbor General Hospital, Torrance, Ca.

Since 1974, 40,012 individuals have volunteered for TSD heterozygote screening in Ca.. Of these, 6,795 are "nonJewish". With an automated serum hexosaminidase (HEX) assay, a tri-variable analysis is possible: Total HEX activity (TA); % HEX A (56°); and nanomoles HEX A (nM): TA x %A. Genotype assignment is based on:

	TA* ± SD	%A ± SD	nM A ± SD
TSD obl. heterozy. (55)	735.5 ± 162.9	38.4 ± 4.8	281.2 ± 69.7
SD obl. heterozy. (14)	423.5 ± 69.6	80.1 ± 3.7	337.3 ± 65.8
"Normal" homozy. (10,000)	785.5 ± 128.6	64.3 ± 3.6	468.1 ± 75.9

* nMoles 4MU produced/hour/ml. serum

Suspect SD carriers (serum TA < 450; %A > 75) and TSD heterozygotes (%A < 50; nM A <420) are confirmed by WBC testing and family studies. The SD gene has been identified in 20 families in this way (4 Jewish). In Jews the gene frequency for TSD is 0.0167 (1:30 carriers) and for SD is 6.0×10^{-5} (1:8304 carriers). In "nonJews" the TSD gene frequency is 0.0035 (1:141 carriers) and for SD, 0.0012 (1:425 carriers).

These data provide the first direct approximations of the gene frequencies for TSD and SD in the Jewish and nonJewish populations. Because of possible nonrandomness in the sample and ancestral uncertainties, these figures should be viewed as reasonable estimates only. Similar analyses with sera from obligate heterozygotes for I-Cell Disease and Mucolipidosis III may allow carrier frequency estimates for these recessive alleles in these populations as well.

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A QUANTITATIVE IN VITRO MODEL FOR THE STUDY OF MUCUS-PRODUCING SUBSTANCES IN CYSTIC FIBROSIS. Lawrence E. Kurlandsky, Betsy G. Bang, Frederik B. Bang and Richard C. Talamo. The Johns Hopkins University, Johns Hopkins Hospital, Departments of Pediatrics and Pathobiology, Baltimore, Maryland.

In vitro assays have demonstrated the presence of a "factor" in the serum of patients with cystic fibrosis (CF) which alters mucus production and ciliary action. A more quantitative assay system is needed. Mucociliated "urn cells", which are found in the coelomic fluid of the marine invertebrate Sipunculus nudus are being used to approach this problem. These cells are easily cultured in their own serum and respond to specific stimuli by secreting mucus tails which vary in rates of response, in quality, and in mean length, depending on the source of the stimulus. This dose-related response can be directly observed in a light microscope, and the length of the mucus tail can be measured. Heated human serum is a known stimulus of mucus production. Thus, human sera from control subjects and patients with CF were tested. Preliminary results show that 18 control sera yielded a mean (± SD) mucus tail length of 1.5 (± 0.21); sera from 12 CF homozygotes yielded a mean mucus tail length of 6.6 (± 1.3), $p < .005$. A consistent response was noted when a given serum was retested in the same urn cell suspension, as well as when a given serum was tested in different urn cell suspensions over a time interval of 3 months. Such a population of discrete mucus-producing cells may provide a useful in vitro model for studying the effects of the putative CF factors on mucociliary action.

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SPECIFIC ^{64}Cu BINDING IN MENKES AND NORMAL SKIN FIBROBLASTS (FB). G.U. LaBadie, N.G. Beratis, P.M. Price, and K. Hirschhorn. Mt. Sinai Sch. Med., and N. Y. State Inst. Basic Res. Mental Retdn., New York, New York.

Menkes FB demonstrate a greater accumulation and a reduced efflux of copper than normal FB. As shown by DNA synthesis, copper was toxic to Menkes FB even at 2 µg/ml which was found stimulatory to normal FB. Treatment of labeled FB with trypsin did not affect the level of ^{64}Cu accumulation. Most of the ^{64}Cu incorporated was bound to a molecule with a MW of approximately 10,000. The amount of radioactivity bound to this molecule was greater in Menkes than in normal FB. A small amount of radioactivity, proportionally greater in normal than in Menkes FB, was bound to a molecule(s) with a MW > 100,000. ^{64}Cu incubated with lysates of normal and Menkes FB bound preferentially to a molecule with a MW of approximately 10,000. By incubating increasing amounts of ^{64}Cu with a constant amount of FB protein, an increasing amount of radioactivity was bound to MW species > 100,000. In a mixture of 0.12µg ^{64}Cu with 4 mg Menkes FB protein, all the radioactivity was bound to the small MW species, whereas in a similar mixture with normal FB, only 70% of the ^{64}Cu was bound to the small MW form, and the remainder to the large MW molecule(s). Even at saturating ^{64}Cu concentrations, the radioactivity bound to the 10,000 MW species was still greater in the Menkes FB. Mixtures of fractions of the labeled large and low MW species with lysates from normal and Menkes FB showed interconversion of the radioactivity between these molecular forms. These data indicate that copper is preferentially bound to a small molecule and that Menkes FB bind more copper than normal FB.

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WAGNER-STICKLER SYNDROME: A GENETIC STUDY. Ruth M. Liberfarb, Tatsuo Hirose and Lewis B. Holmes, Harvard Medical School, Mass. Gen. Hosp., Children's Service and Eye Research Institute of the Retina Foundation, Boston.

Based on our study of 32 affected individuals in 10 families, we suggest that the Wagner and the Stickler syndromes could be the same disorder. Both the Wagner and the Stickler syndromes are autosomal dominant disorders with a similar pattern of eye abnormalities, including myopia, presenile cataracts, strabismus, vitreo-retinal degeneration, retinal detachment and retinoschisis. Only the Stickler syndrome has been associated with non-ocular problems, such as cleft palate, micrognathia, mid facial hypoplasia, hearing loss and degenerative arthritis. All of the index cases in our study were ascertained because of their retinal symptoms as having the Wagner syndrome. Three families were included in a report on Wagner syndrome in Arch Ophthal. 89:176, 1973 by Hirose et al.

There is a wide variability in the associated features and a slow progression of symptoms. Many affected individuals have similar facial features. Early recognition improves the prognosis for vision. Most of these families were unaware of the genetic nature of the Wagner-Stickler syndrome in spite of the fact that several family members in more than one generation were affected. Most specialists involved in their care are unaware of this disorder. Histologic section of enucleated eyes from two affected individuals are similar.

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SEROTONIN UPTAKE AND SODIUM UPTAKE IN Na^+ DEPLETED AND NON-DEPLETED PLATELETS IN DOWN'S SYNDROME (D.S.) Ernest E. McCoy and Louise Enns. Department of Pediatrics, University of Alberta, Edmonton, Alberta.

This study was undertaken to determine the mechanism of decreased rate of serotonin (5HT) uptake into D.S. platelets. We have shown that in D.S. platelets, 5HT uptake, Na^+/K^+ ATPase activity and rate of outward movement of Na^+ are decreased and Na^+ content increased. As 5HT is believed to be co-transported with Na^+, its rates of uptake into Na^+ depleted and non-depleted platelets as well as rates of Na^+ uptake were studied in normal and D.S. platelets. Platelets were isolated from D.S. and control subjects and depleted of Na^+ by incubation in a Na^+ free medium in which choline chloride replaced Na^+. Platelets were Na^+ repleted by addition of Na^+ to the incubation buffer. Na^+ uptake was studied by using 22 Na and 5HT with 14C 5HT over 0.5 to 5 min. The rate of Na^+ uptake into control platelets was decreased, 107.3±9.9 nmoles compared to 149.0±15.4 nmoles/hr./10^9 platelets in D.S. ($p<.05$). 5HT uptake in contrast was decreased in D.S. 16.2±2.8 compared to 27.2±3.3 nmoles/hr./10^9 platelets in controls ($p<.025$). In Na^+ depleted platelets 5HT uptake was increased to 153.8±20.9 nmoles in controls compared to 66.0±5.3 nmoles/hr./10^9 platelets in D.S. ($p<.005$). Although inward transport of Na^+ was increased in D.S., the uptake of 5HT was decreased in both non Na^+ depleted and Na^+ depleted platelets. 5HT uptake may be independent of or linked in a very specific way to Na^+ transport in D.S. platelets. There may be a specific defect of 5HT uptake in D.S. platelets.