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Genetic testing for Niemann-Pick Type C disease. K. Snow, W.D. Park, P.A. Lundquist, C. Walsh Vockley, M.C. Patterson, P.S. Karnes, J.F. O'Brien. Mayo Clinic, Rochester, MN.

Niemann-Pick Type C (NPC) disease is an autosomal recessive lysosomal storage disorder that is characterized biochemically by sequestration of unesterified cholesterol and glycolipids in endosomal and/or lysosomal vesicles with consequent delay in cholesterol esterification. Clinical manifestations include progressive neurodegeneration, variable hepatosplenomegaly and vertical supranuclear gaze palsy. Death often occurs during childhood or early adulthood. NPC is a panethnic disorder with an estimated prevalence of 1 in 150,000. In approximately 95% of families the disease is linked to the NPC-1 gene at 18q11. This gene, isolated in 1997, contains 25 exons encoded by 3.9kb cDNA. Using multiplex PCR and CSGE to screen for mutations in NPC-1, we have tested genomic DNA from 53 unrelated affected individuals. Putative mutations were identified on 64 of 108 (59%) disease alleles and included 38 different DNA alterations located throughout the gene. Types of mutations included: missense (27), nonsense (1), frameshift (5), in-frame deletion (2) and splice site mutation (3). Recurrent mutations were I1061T (allele frequency 19/108, 18%), P237S (allele frequency 4/108, 3.7%), and delI271 (allele frequency 2/108, 1.9%). In addition to the putative mutations, 6 polymorphisms were identified. The finding of a high degree of mutation heterogeneity with many missense alterations creates difficulties for the clinical application of mutation testing in NPC. Although we can determine if missense alterations are in proposed functional domains or at sites conserved across species, we cannot be certain of the pathogenicity of such alterations. DNA alterations identified in affected patients can be used as linkage markers to determine carrier status of at risk relatives. However, the diagnosis in the affected individual must be confirmed by biochemical testing, and must include complementation analysis to establish that the defect is in NPC-1. Mutation analysis for individuals from the general population (e.g. partners of NPC carriers) is likely to result in significant dilemmas in interpretation of results. Funded by a grant from the Ara Parseghian Medical Research Foundation.

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The HFE 5569A allele defines a low-risk haplotype for hereditary hemochromatosis. M.J. Somerville, K.A. Sprysak, M. Hicks, B.G. Elyas, and L. Vicen-Wyhony. University of Alberta and UA Hospital, Edmonton, Alberta, Canada.

Hereditary hemochromatosis (HH; MIM 235200) is an autosomal recessive disorder of iron metabolism that is estimated to affect approximately 1 in 300 individuals of northern European origin. Several missense mutations have been reported in the HFE gene including: C282Y accounting for 80% to 90% of HH chromosomes, H63D which has been found on 40% to 70% of non-C282Y HH chromosomes, and S65C which has been found on 5% to 10% of non-C282Y HH chromosomes. In addition, HFE single nucleotide polymorphisms (SNPs) have been identified, including 5569G/A in intron 4. We analyzed 336 unrelated individuals that had been referred for hereditary hemochromatosis molecular testing. Each sample was tested for C282Y, H63D, S65C, and 5569G/A status, and data were compiled relative to clinical status. All sequence variants appeared to be in linkage disequilibrium, such that there were no individuals with any combination of more than two of these nucleotide changes. Allele frequencies for Y282, D63, and C65 were significantly greater in clinically affected individuals (as has been previously reported), whereas the frequency of the 5569A allele was significantly elevated in unaffected individuals in our population ($P < 0.000001$). These findings suggest that 5569G/A genotype screening can be used to modify the probability of HH when mutation screening results are inconclusive.

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Mohr-Tranebjaerg Syndrome is an X-linked Recessive Disorder Characterized by Mitochondrial Dysfunction Associated with Neuronal Cell Death. *L. Tranebjaerg[1], S. Lindal[1], S. Merchant[2], OC. Ingebretsen[1], B. Hamel[3], V. Fung[4], M. Hayes[4], C. Koehler[5], O. Nilssen[1], M. van Ghelue[1].* 1) Dept Medical Genetics, Dept Pathol, Dept Clinical Chemistry University Hosp, Tromsoe, Norway; 2) Temporal Bone Registry, Massachusets Gen Hosp, Boston; 3) Dept Human Genet Univ Hosp Nijmegen, Netherlands; 4) Dept Neurol, Westmead Hosp, Westmead, Australia; 5) Biozentrum Basel Univ, Basel, Switzerland.

Mohr Tranebjaerg syndrome (MIM 304700) is clinically well characterized and shown to be due to frameshift/stop mutations in the DDP gene (Tranebjaerg L et al, J Med Genet 32; 257-263, 1995; Jin H et al, Nat Genet 14; 177-180, 1996). We present the updated spectrum of mutations in the 7 families recognized from Norway, USA, Spain, Denmark, Australia and the Netherlands each having a private DDP mutation. Recently, a DDP homologue (TIM 8) in yeast was shown to be involved in mitochondrial membrane protein transport (Koehler C et al, PNAS; 99: 2141-6, 1999) which implies that human deafness-dystonia syndrome is likely to be a mitochondrial dysfunction associated with neurodegenerative disease. We present clinical neuropathological and biochemical evidence supporting that this human deafness-optic atrophy-dystonia syndrome is caused by mitochondrial dysfunction.