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The locus for autosomal dominant renal Fanconi Syndrome maps to the long arm of chromosome 15. U. Lichter-Konecki[1], K.W. Broman[2], R. Dart[3], E. Blau[3], D.S. Konecki[1]. [1]Center for Medical Genetics, Marshfield Medical Research Foundation, Marshfield, WI; [2]Dept. of Biostatistics, School of Hygiene and Public Health, John Hopkins University, Baltimore, MD; [3]Marshfield Clinic, Marshfield, WI.

Familial renal Fanconi Syndrome is a genetic model for the study of the pathophysiology of renal tubular transport. Affected individuals are normal at birth. However, during the second decade of life they develop polyuria, and loss of proximal tubular function results in rickets. With increasing age, these individuals may develop renal failure. Therapy for renal Fanconi syndrome consists of symptomatic supplementation therapy, dialysis, and kidney transplantation. The isolation of the affected gene should initially facilitate postnatal and prenatal diagnosis of renal Fanconi syndrome. Long term, the isolation of this gene and its gene product will allow the study of the pathophysiology of renal Fanconi syndrome. Such studies should lead to a better understanding and consequently a better treatment of this entity. Through knowledge about the pathophysiology of this disorder new drugs may be developed to treat renal tubular transport disorders. We were able to map the locus for autosomal dominant familial renal Fanconi syndrome to the long arm of human chromosome 15 by genotyping a large central Wisconsin pedigree by performing a whole genome scan with 367 highly polymorphic simple sequence repeat (SSR) markers. A maximum LOD score of 3.01 was calculated using the LINKAGE program package (version 5.03), with the analyses conducted assuming a fully penetrant autosomal dominant mode of inheritance. Analysis of an additional 29 markers flanking D15S659 has narrowed the interval to about 3 cM, with the highest LOD observed being 4.43. The fine mapping of the locus for autosomal dominant renal Fanconi Syndrome is continuing, the goal of which is to sufficiently narrow the region to allow the isolation of the associated gene through a positional cloning approach.

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Detection of a *de novo* mutation in a family with SMA Type I: The importance of dosage testing. J. McGowan-Jordan[1], S. Zeesman[2], D.T. Whelan[2], P.N. Ray[3], T.L. Stockley[3], T. Prior[4], N.L. Carson[1]. [1] Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, [2]McMaster University Medical Centre, Hamilton, ON, Canada, [3]Hospital for Sick Children, Toronto, ON, Canada, [4]Ohio State University, Columbus, OH.

Type I spinal muscular atrophy is a devastating neurodegenerative disease with onset by 6 months of age and death by the age of two years, usually due to respiratory infection. Homozygous deletions of the SMNtel, but not the SMNcen, gene have been identified in 95% of SMA patients. These genes map to chromosomes 5p13 and are within a large inverted repeat which includes the NAIP gene, the telomeric copy of which is also deleted in a large proportion of SMA type I patients.

We have investigated a family, in which there had been an affected child who was homozygously deleted for SMNtel and NAIP exon 5, to determine the disease status of a fetus. Analysis of cultured amniocytes indicated that the fetus is not homozygously deleted for SMNtel or NAIP. Several markers in the SMN/NAIP region were used to rule out maternal contamination of the amniocytes. During this process, it was noted that the fetus and the affected child had similar haplotypes but the paternal chromosome in the affected child carried a recombination. This recombination is associated with a deletion of several alleles of two multiallelic markers, AG1 and CATT. Dosage analysis revealed that the mother is an SMA carrier with only one copy of SMNtel. In contrast, the father has 2 copies of SMNtel, suggesting that he is not a carrier of an SMNtel deletion. Rather, the paternal allele in the affected child probably resulted from a recombination event during which there was simultaneous deletion of the SMNtel gene along with some AG1 and CATT alleles. These data significantly lower the SMA recurrence risk for this family. This case highlights the necessity of using dosage information when assessing recurrence risk in SMA families.

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Association of G-protein β3 subunit C825T variant (Gβ3S) and heart valve abnormalities in obese patients treated with fenfluramine-phentermine. L. Ning; J.P. Eichelberger, B.C. Berk, M. Qi. Center for Cardiovascular Research, University of Rochester Medical Center, Rochester NY.

Obesity is associated with serious health risks, including an increased incidence of heart disease, stroke, and hypertension. Appetite-suppressant medications such as fenfluramine-phentermine (fen-phen) have been used for several decades to treat obesity. Recently, fen-phen has been suggested to increase the incidence of cardiac valvulopathy. Among potential mechanisms, increased signal transduction by G protein coupled receptors such as the serotonin receptor (5HT1C) may be important. We hypothesized that patients with the C825T polymorphism would be at higher risk for fen-phen associated disease, because the 825T allele is associated with the generation of a novel splice variant, enhanced intracellular signal transduction, and arterial hypertension. We re-evaluated 33 patients who were treated with fen-phen during a randomized crossover trial in 1983. All patients had no history of heart disease at the onset of the original study. During reevaluation each patient completed a questionnaire, underwent cardiac auscultation, had a complete echocardiographic evaluation, and Gβ3S C825T allele genotyping. Fifteen age-matched untreated obese patients served as controls. A significant association between the 825T allele and obesity was observed (TT+TC = 85.4% in this group of obese patients, compared to 25% prevalence in the general population [Siffert, Nat. Genet 18:45,1998]) similar to results reported by Siffert (J Am Soc Nephrol 10:1921,1999). There was no difference in the prevalence of 825T allele among patients with cardiac valvulopathy (TT+TC: 6/8 [75.0%]) compared to patients without valvulopathy (TT+TC: 22/25 [88.0%]) in fen-phen treated patients. Prevalence of 825T allele was similar in untreated control patients (TT+TC: 13/15 [86.7%]). The TC genotype was significantly increased among treated patients who developed cardiac valvulopathy (5/8, 62.5%) compared to treated patients without valvulopathy (10/25, 40.0%, $p < 0.01$) or control patients (7/15, 46.7%, $p < 0.01$). This observation, if replicated in larger studies, suggests a genetic contribution to the cardiac effects of fen-phen.

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CFTR Mutations in Chilean patients with cystic fibrosis. G.M. Repetto[1], I. Flores[1], C. Lobo[1], M.L. Boza[2], M.A. Perez[3], E. Guiraldes[1], P. Harris[1], I. Sanchez[1]. [1]P. Universidad Catolica de Chile, [2]Hospital San Borja-Arriaran, [3]Hospital Exequiel Gonzalez Cortes, Santiago, Chile.

Chilean population is a complex admixture of Amerindian, European and other ancestries. The estimated frequency of cystic fibrosis (CF) in the country is 1: 4,000, but it has been postulated that underdiagnosis is significant and may amount up to 50% of the cases. We have evaluated the presence and frequency of 11 of the most common CFTR mutations, according to the International CFTR Mutation Consortium, in 18 unrelated children with CF using an ARMS-based method. Mutations analyzed were deltaF508, delta1507, G542X, G551D, G553X, R560T, R117H, W1282X, N1303K, 1717-1G->T and 621+1 G->T.

The type and frequency of mutations found were: delta F508, 17 % total alleles; W1282X, 19%; G551D, 3 %; G542X, 3%; undetected 58%. The other mutations were not observed. In five patients, no mutations were found. The low detection rate is similar to that described in other Hispanic populations, emphasizing that fact that there may be mutations unique to these ethnic groups. Addition of other common mutations to our panel, as well as identification of those specific to our population may increase the diagnostic yield and aid in studies to determine the carrier rate and incidence of the disease. (Funded by a grant from the Child Health Foundation, AL)