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An unexpected female patient within a classical Lesch-Nyhan family.
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The Lesch-Nyhan (LN) disease is a genetic disorder of purine metabolism caused by defective activity of the enzyme Hypoxanthine-guanine PhosphoRibosyl Transferase (HPRT). Affected individuals have a striking phenotype characterized by hyperuricemia and uricosuria, spasticity, involuntary movements, developmental disability and self-injurious behavior. The HPRT gene is located on the long arm of the X chromosome (Xq26) and the pattern of inheritance is X-linked recessive. The classical phenotype occurs exclusively in males, while heterozygous, carrier females are generally normal.
We analyzed an Argentine family in which there were male and female siblings with clinically identical classic features of Lesch-Nyhan disease. The mother and an older daughter were carriers with normal phenotypes. We identified the HPRT mutation in the family. It is a C->T transition at position 508 of the cDNA that changes the CGA codon for Arg(169) to the TGA stop codon. The female patient was karyotypically normal and heterozygous for the mutation. She inherited the HPRT mutation from her mother, but she also had unexpected nonrandom inactivation of the paternal X chromosome carrying the normal HPRT gene. This additional genetic alteration is the cause of the clinical expression of the disease in this female patient.
Three cases of female patients with classical LN clinical features have been previously reported. Each of them showed a different *de novo* molecular alteration that led to a specific HPRT enzyme defect, along with a mechanism of nonrandom inactivation of the X chromosome carrying the normal copy of the HPRT gene. Our family differs in that the HPRT mutation was inherited in at least three individuals, one of whom is our female case. Like the other affected females, she also shows nonrandom inactivation of the normal X chromosome.

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Primary Ciliary Dyskinesia : A search for the responsible genes through linkage and candidate gene approaches. C.D. DeLozier-Blanchet[1], L. Bartoloni[1], C. Gehrig[1], U. Radhakrishna[1], M Meeks[2], G. Duriaux-Sail[1], A. Maiti[1], P.A. Guerne[3], H.Walt[4], RM Gardiner[2], S.E. Antonarakis[1], J.L.Blouin[1]. [1]Division of Medical Genetics, and [3]Division of Rheumatology, Geneva University Hospital, Switzerland, [2]University College London, England and [4]Dept. of Obstetrics & Gynecology, Zurich University Hospital, Switzerland.

Primary Ciliary Dyskinesia (PCD) is an autosomal recessive disorder in which dysmotility to immobility of cilia and flagella result in upper respiratory tract infections, bronchiectasis and male sub-fertility. About half of patients have situs inversus (Kartagener syndrome). Extensive genetic heterogeneity is expected given the complex ultrastructure of cilia and flagella. Recently, the first report of mutations in a specific gene (DNAI1) were reported in a single Kartagener patient (Pennarun et al., AM J HUM GENET 65 suppl, A35, 1999). In Switzerland and as part of a European consortium, we collected DNA samples from 61 families, 31 of which had two or more affected members. A genome-wide linkage search was performed using 188 evenly-spaced microsatellites. Linkage analysis was performed in all families with two affecteds, and in sub-sets of families with situs inversus and with dynein arm deficiency. Data was analyzed using both parametric and non-parametric methods. Although no marker showed statistically-significant values for linkage, several chromosomal regions (4q,5p,8p,16p, and 19q) were identified with suggestive scores. These findings support the hypothesis that mutations in several distinct genes may produce the PCD/ Kartagener phenotypes. As dyneins are good candidates for this disorder, we are currently screening PCD patients for mutations in dynein-related genes mapping to the pinpointed chromosomal regions.
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Mitochondrial DNA mutations in chilean patients with Leber Hereditary Optic Neuropathy (LHON). R. Fadic[1], C. Lobos[1], M. Schweitzer[2] and C. Luco[1,2]. [1]P. Universidad Católica, and [2]Instituto Asenjo, Santiago. Chile.

LHON is a cause of blindness in otherwise healthy young persons, mainly men. Three mitochondrial DNA (mtDNA) mutations in the positions 11778, 3460, and 14484, are considered primary for this condition. All three lead to an amino acid change in a mitochondrial respiratory chain Complex I subunits. These mutations account for more than ninety percent of LHON cases in Caucasian and Japanese populations. The frequency of these mutations in other ethnic groups is not well studied. Approximately eighty five percent of Chilean individuals with Hispanic last names have Amerindian mtDNA haplotypes.
We studied the presence of these mutations and the mDNA haplotype by RFLP in Chilean patients with LHON.
Fifteen patients were included in the study. Three patients had the 11778 mutation, three had the 14484 mutation. None of the primary mutations was found in the remaining nine patients. All of the patients have Amerindian mtDNA haplotype. These results suggest that these two mutations have originated independently in different mtDNA haplotypes. There are probably different mtDNA mutations that explain the rest of our patients. Funded by Fondecyt 1990514.

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The frequency and clinical significance of the S1235R mutation in the Cystic Fibrosis Transmembrane Conductance Regulator gene: results from a collaborative study. G.L. Feldman[1,2], K.G. Monaghan[1], G.M. Barbaratto[3] and K. Snow[3]. [1]Henry Ford Hospital, Detroit, MI, [2]Wayne State University School of Medicine, Detroit, MI and [3]Mayo Clinic, Rochester, MN

More than 850 mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene have been reported to the Cystic Fibrosis (CF) Consortium. A missense mutation, S1235R, was originally reported in a CF patient with a second mutation (G628R) on the same chromosome. The clinical significance of S1235R was not clear. S1235R is not among the commonly reported mutations, and it is not routinely screened for in most laboratories. However, we have identified this variant in our laboratories at a higher frequency than many of the other CF mutations. Among more than 3,000 patients tested for either a possible diagnosis of CF or to determine CF carrier status, we identified 50 patients heterozygous for S1235R. No patients were homozygous for S1235R. The allele frequency of S1235R in this population (~1%) was higher than that of the G551D or G542X CF mutations. Patients found to carry S1235R ranged in age from 1 day to 73 years. Indications for testing included rule out CF (15 cases), prenatally diagnosed echogenic bowel (2 cases), meconium ileus/obstruction at birth (3 cases), carrier screening with a positive family history (11 cases), carrier screening with a negative family history (17 cases) and unknown (2 cases). Four patients were compound heterozygotes for a second CFTR mutation: 2 cases (one family) were N1303K/S1235R and 2 unrelated cases were ΔF508/S1235R. Clinical data on those patients will be presented. No patient tested so far (N=31) carried the G628R CFTR mutation.
Our data suggests that S1235R, when combined with a second CF mutation, may be pathogenic, although phenotypic manifestations appear to be variable. However, the possibility that this represents a rare polymorphism cannot be discounted completely. Genetic counseling issues are difficult when S1235R is identified, even in the presence of a second known mutation, especially in prenatal cases.