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FGFR3 Mutations K650N and K650Q Cause Hypochondroplasia.
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More than 50% of individuals with hypochondroplasia are heterozygous for mutations at a single FGFR3 nucleotide that result in N540K substitutions. Although genetic heterogeneity has been demonstrated in several families, it is likely that FGFR3 mutations other than N540K also cause hypochondroplasia. We have screened more than 65 individuals with suspected clinical diagnoses of hypochondroplasia (but who do not have N540K mutations) for mutations in FGFR3 exon 15 that disrupt a *Bbs*-I restriction site. We report here the discovery of 3 novel mutations (G1950T:K650N, G1950C: K650N & A1948C: K650Q) occurring in 5 individuals with clinical features of hypochondroplasia. The phenotype of these individuals tends to be milder than that of individuals with N540K mutations. Total height deficit was less [K650N/Q = -2.09 SD +/- 0.67 (n=5), N540K = -3.25 SD +/- 1.09 (n=36): P <0.05] and shortening of the metacarpals and proximal digits was less pronounced. In addition, other radiographic features such as narrowing of the lumbar interpedicular distance and overgrowth of the fibula tended to be milder. Mutations in the K650 codon of FGFR3 that cause thanatophoric dysplasia type II (K650E) and SADDAN syndrome (K650M) result in ligand independent constitutive activation of FGFR3 tyrosine kinase. The K650N and K650Q mutations activate FGFR3 tyrosine kinase to similar extents however the degree of activation is more than 10 fold less than that of the K540E and K650M mutations. These results highlight the importance of the K650 codon in FGFR3 function.

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Knowledge and attitudes about carrier testing for hemophilia A among patients and their relatives. N Callanan, T. Jennings-Grant, C. Lakon, T. Spinney, J R. Sorenson. University of North Carolina

127 patients with hemophilia A were asked to assist in recruiting at risk female relatives for a study to assess their knowledge and attitudes regarding carrier testing. Of these 21(17%) agreed to complete a questionnaire and 66 (52%) agreed to participate by 1) supplying a blood sample for DNA analysis, 2) completing a questionnaire, 3) providing family history and 4) contacting at risk female relatives to inform them about the study. Of the 87 patients who completed the questionnaire, 58% had previously received information about the inheritance of hemophilia. 71% believed they had an obligation to inform at risk relatives, 81% thought that carrier testing was important and 58% had discussed carrier testing with relatives in the past. 88% did not think that being asked to contact relatives was an invasion of privacy. 65 patients were tested and a mutation was identified in 50 (77%). 34 provided contact information for some or all of their 341 potentially eligible relatives. 79 (23%) of the relatives declined, 37(11%) could or would not be contacted by the patient, 62 (18%) were excluded because they did not meet study deadlines and 163 (48%) agreed to be contacted by the research team. We contacted 162 at risk relatives. 5(3%) were ineligible, 13(8%) declined all participation, 26(16%) declined testing but agreed to be interviewed, and 113(70%) agreed to have counseling, testing, and complete at least one interview. Of the 5 (3%) obligate carriers, 1 agreed to be interviewed. A total of 140 women completed one or more interviews. 90% had not previously received genetic counseling, 62% had not previously been tested, and 52% thought their chance of carrying a hemophilia gene was extremely low or low. 87% were interested in knowing about carrier testing. 42% reported having a "close" relationship with their affected relative. 98% did not think that our asking their relative with hemophilia to contact them was an invasion of privacy. Of 115 who visited a doctor within the past year, 87% did not specifically discuss their possible carrier status. Data on individuals participating in this ongoing NHGRI funded study suggest: 1) patients contacting relatives about carrier testing is not viewed as an invasion of privacy, 2) most patients think carrier testing is important and have discussed testing with relatives, and 3) although relatives prefer to know about testing, most had not discussed testing with their physician within the last year nor had they had genetic counseling. The significance of these data on research participation and possible implications for clinical practice will be discussed.

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Unilateral congenital lymphedema with intestinal lymphangiectasia, elevated liver transaminases, and hypopigmentation. WM Campbell, JM Noel, LS Martin. Madigan Army Medical Center, Tacoma, WA

Congenital lymphedema occurs with intestinal lymangiectasia in several syndromes, including those described by Turner, Noonan, and Hennekam. We report a 16 year-old Filipino female with an unusual presentation of congenital lymphedema. She has had persistent right facial puffiness since birth. She later developed hypopigmented patches and increased circumference of her right extremities. Liver transaminases became persistently elevated at age 15 years. Laboratory evaluation for infectious and other causes of her hepatitis was negative. Past medical history was otherwise unremarkable. Family history was significant for a maternal aunt with hypopigmented patches and several relatives with premature graying. No relatives had lymphedema, autoimmune disorders, or liver disease. Physical examination revealed right facial fullness and scattered coarse, white scalp hairs but no dysmorphic features. Pretibial pitting edema was present on the right, with mild pitting and ridging of the nails. Right upper and lower extremity circumferences were increased compared to the left, with no limb length discrepancy. Multiple ½ to 1-cm areas of hypopigmentation were noted on the extremities. Radiographs of the extremities showed increased reticulation in the subcutaneous fat on the right. Magnetic resonance imaging revealed right-sided asymmetry of subcutaneous fat. Liver biopsy demonstrated chronic, nonspecific inflammation. Duodenal biopsy showed lamina propria lymphangiectasia. This patient's condition seemed unique in that she had lymphedema of her entire right side, with the left side clinically and radiographically spared. We postulate that a developmental field defect of the embryonic mesenteric lymph sac and the right thoracic duct and lymph sacs accounts for both her unilateral congenital lymphedema and her intestinal lymphangiectasia. The constellation of findings in this patient, lymphedema, intestinal lymphangiectasia, elevated liver transaminases, patchy hypopigmentation, and coarse, white scalp hairs, has not been described in the English-language literature and may represent a new syndrome.

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Clinical findings in mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE) J.A. Chacin.[1] C. Martinez-Basalos [1], L. Pineda[1], S. Gonzalez[1], A. Morales de Machin [1], N. Ramos [1], O. Molina [2], I. Soto [2], J. Cardozo[3], Castillo M.[4] [1] Genetic Department at Zulia University (LUZ) [2] Department of Neurology, University Hospital[3] Department of Neuroanatomy[4] Ophthalmology Residency Program, School of Medicine. LUZ. Maracaibo, Venezuela.

Introduction: OXPHOS diseases are a heterogeneous group of disorders caused by mutations in mitochondrial or nuclear DNA. They display either matemal or mendellian inheritance. We describe the clinical features of four patients with MENGIE. Material and methods: clinical presentation: four patients from two families: Family A: 2 affected siblings, male and female, born from unrelated healthy parents who had healthy children in posterior marriages. The male, usually thin, developed ptosis, ophthalmoparesis, visual impairment and muscle weakness at age 13 years. Deafness and diarrhea became evident at age 37. The female developed diabetes in addition to the same clinical features. Family B: two affected children, male and female, born from noconsanguineous healthy parents. They did not gain weight after age 7 years with progressive decrease in muscle mass. They still walked at age 15, nevertheless, they had difficulties climbing stairs. In addition, they also developed ptosis and opthalmoparesis. At the age of 17 the male developed frequent diarrhea and ceased to walk. Clinical Evaluation: all the patients showed both proximal and extraocular muscle weakness with onset before the age of 20 years. Deafness, diarrhea and visual impairment appeared later. The clinical course was worse in the males. Laboratory studies showed increased levels of lactate and pyruvate, normal CK, decrease of serum l-carnitine. Brain MRI revealed Increased T2 signals. EMG revealed myogenic or neurogenic abnormalities and nerve conduction alterations. Muscle biopsy showed proliferation of abnormal mitochondria. Discussion: an autosomal recessive inheritance pattern was inferred because of healthy parents, recurrence in sibs and both genres being affected. The diagnosis was based on the recognition of the phenotype, the histological and ultraestructural mitochondrial abnormalities, biochemical tests, however, the diagnosis of difficult, non-classic cases is possible only by DNA analysis.