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### Identification of mitochondrial mutation (tRNA<sup>lys</sup>) & genetic counseling in a family with MERRF syndrome

HI Kim<sup>1</sup>, SI Park<sup>1</sup>, MI Ha<sup>1</sup>, CW Kim<sup>2</sup>, JS Kim<sup>2</sup>

Medical Genetics<sup>1</sup>, Neurology<sup>2</sup>, Ajou Univ Sch of Med, Suwon, Korea

MERRF (Myoclonus, Epilepsy Ragged Red Fiber) syndrome is one of well characterized mitochondrial encephalomyopathy with maternal inheritance due to a heteroplasmic A-to-G point mutation at bp 8344 in mtDNA, in the gene coding for tRNA<sup>lys</sup>, in majority of cases (>80%). At present, no effective treatment is available for this progressive disabling neuromuscular disease with identification of mitochondrial mutation, therefore the development of effective genetic counseling is very much in need for the pt and family with the mutation. Yet the nature of heteroplasmy of mitochondrial mutation make the genetic counseling limited value with difficulty in predicting clinical phenotype. We have identified mt mutation of tRNA<sup>lys</sup> in a 31 y/o single female with clinical Dx. of MERRF syndrome and in her 4 other family members: a 29 y/o married sister with mild myoclonus without epilepsy who wants to start family, a 34 y/o unaffected sister who is seeking genetic counseling for her two normal children. Mitochondrial mutation was determined by RFLP of PCR DNA product with mismatched primer following Nae I restriction enzyme digestion of Genomic DNA from PB. The mutation load (Ratio of mutant DNA:nl DNA) was found to be variable in the family: 60% in the proband, 80% in mildly affected sister and 50% in unaffected sister with 80% in a 7 y/o her daughter and 60% in a 10 y/o her son. Therefore no positive relationship between mutation load in PB and clinical phenotype was found nor mutation load in the mother and phenotype of offspring can be predicted in this family. The genetic counseling for prenatal and presymptomatic DX may offer only limited value for the family.

Further study including mutation load in muscle biopsy along with prospective follow up study of the family may provide additional Data which can be informative in genetic counseling.

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Microgastria in the Genetic Clinic.  
B.G. Kousseff, University of South Florida

Microgastria is a rare developmental anomaly of the gastrointestinal tract that occurs during organogenesis (5<sup>th</sup> to 9<sup>th</sup> week of gestation). It could be a solitary malformation or part of multiple anomalies (syndromic microgastria). Prenatally absent/ tiny stomach bubble is the sonographic sign. Between January 2, 1982 and April 15, 1999 through the University of South Florida Genetic clinics there were ten probands with suspected/confirmed microgastria. They were part of the 35414 probands/families evaluated. Four were seen through the pediatric genetic clinic. All had microgastria with associated anomalies: JC a Mexican one-year-old boy had it with extensive partial albinism, mixed bilateral hearing loss, blepharophimosis, abnormal nasolacrimal ducts, ASD, pulmonic stenosis, pectus carinatum, asymmetric brachydactyly, mild mental retardation and 46, XY karyotype. JH was a newborn Caucasian girl with polyhydramnios, intrauterine growth retardation, TE fistula, tetralogy of Fallot, partial situs-inversus, second and third toe syndactyly and 46, XX karyotype. CC was a premature newborn Caucasian girl with polyhydramnios, TE fistula, spleen with extraneous lobe, GE reflux that required Nissen fundoplication, pectus carinatum and left inguinal hernia. DW was a newborn Caucasian boy with left cleft lip and palate, GE reflux, ectrodactyly including lobster foot, failure to thrive, short stature and 46, XY karyotype. All required frequent small feedings and DW had surgery to create a larger stomach.

PS, LM, MM, RC, SS and CS were seen through the prenatal clinic/fetal board registry. On targeted sonograms their fetuses did not show a "stomach bubble". The male fetus of PS had Trisomy 21 with single umbilical artery and polyhydramnios; a stillbirth took place (PS developed class A1 diabetes mellitus during the gestation). LM had a stillborn girl with anencephaly, sacral spina bifida and cleft lip. Autopsies of the stillborns were declined. The 46,XX fetus of MM showed also single umbilical artery and polyhydramnios. The fetuses of RC, SS and CS did not show other abnormalities but all failed to return to the clinic.

Comparing these pediatric/genetic and prenatal patients it is obvious that postnatal genetic evaluations are a must whenever microgastria is suspected. Without them "no stomach bubble" may or may not represent microgastria. The same applies to the stillborns without autopsies. The "absent bubble" is a sonographic impression which requires confirmation. Otherwise overdiagnosis of microgastria is taking place.

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### Clinical and Molecular Studies in a large unique family with Limb-Girdle Muscular Dystrophy and Paget Disease of Bone. V.E. Kimonis<sup>1</sup>, M.J. Kovach<sup>1</sup>, A. Salam<sup>4</sup>, S. Leal<sup>4</sup>, B. Waggoner<sup>1</sup>, K. Davis<sup>1</sup>, R. Khardori<sup>1</sup>, and D. Gelber<sup>2</sup>

<sup>1</sup>Division of Genetics and Metabolism, Department of Pediatrics, <sup>2</sup>Department of Internal Medicine, <sup>3</sup>Department of Neurology, Southern Illinois University-School of Medicine, Springfield, <sup>4</sup>Lab of Statistical Genetics, Rockefeller University, New York

A large Central Illinois family with Limb-Girdle Muscular Dystrophy (LGMD) and Paget disease of bone (PDB) includes 9 affected individuals (6 M, 3 F) ranging in ages from 33 y to 64 y. Onset of the disorder is early, at a mean age of 35 y with bone pain in the hips, shoulders and back, weakness and atrophy of the hip and shoulder girdle muscles, and absent or reduced deep-tendon reflexes. Laboratory investigation in the affected individuals indicates elevated alkaline phosphatase (mean 455, range 93-1508 (normal 30-130 mg/dl), and CPK levels (mean 273, range 60-1145 (20-222 mg/dl). High-resolution karyotype did not identify a microdeletion syndrome. Muscle biopsies in 5 individuals revealed non-specific myopathy with vacuolar myopathy only seen in the oldest male. Affected individuals die prematurely from progressive muscle weakness, cardiomyopathy and cardiac failure in the forties to sixties.

LGMD encompasses a genetically and clinically diverse group of disorders. Twenty-two genetic loci were excluded in this family by linkage analysis performed in 9 affecteds, 13 unaffecteds and 1 spouse with 4 autosomal dominant and 8 autosomal recessive LGMD loci, the Edstrom myopathy and ALS loci, 2 Paget disease loci and 6 cardiomyopathy loci, thus supporting our hypothesis that this family displays a genetically distinct disorder. Linkage analysis of haplotype data generated by Marshfield genotyping Center will be presented.

Review of the literature reveals three similar associations of neuromuscular and Paget disease. Caughey et al (1957) described a family suffering from dystrophia myotonica and familial PDB. Tucker et al (1982) identified a family with autosomal dominant amyotrophic lateral sclerosis and PDB, and McBride et al (1966) found an association of PDB and a limb girdle type of muscular dystrophy in four of six siblings. Early demise from cardiomyopathy was not a feature in these families. Paget disease is known to cause high output cardiac failure and may therefore be contributing to the early demise if untreated. Treatment of Paget disease is very successful with bisphosphonates. A treatment protocol with risedronate, coenzyme Q and antioxidants is in progress to evaluate the effects on Paget, muscular dystrophy, and cardiomyopathy. Identification of the specific gene mutation, however, may permit more specific treatment protocols.

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A new case of hepatic glycogen synthase deficiency, biochemical findings and comparison with reported cases. A.M. Laberge<sup>1</sup>, G. Mitchell<sup>1</sup>, G. Van de Werve<sup>2</sup> and M. Lamber<sup>1</sup>. <sup>1</sup>Hôpital Sainte-Justine, Montréal, Québec, Canada, <sup>2</sup>Département de Nutrition, Faculté de Médecine de l'Université de Montréal, Québec, Canada.

Hepatic glycogen synthase deficiency (GSD-0) is an autosomal recessive disorder first described in 1963. Fifteen cases in seven different families have been reported. Mutations in GYS2, the gene coding for liver glycogen synthase, were found in the four families studied. We report a new case of GSD-0 in a female patient born to healthy non-consanguineous French Canadian parents. She was referred for a family history of hyperlipidemia at 7 years of age. In addition to increased plasma total cholesterol and triglyceride levels, workup revealed fasting hypoglycemia and ketonuria. Her only complaint was morning headaches. Growth and development were normal. Physical exam including neurological exam was normal. Cerebral MRI and EEG were normal. Biochemical findings consistent with the diagnosis included fasting hypoglycemia, ketonemia and hypotalaninemia, and postprandial hyperlactatemia and elevated plasma branched chain amino acid levels. Liver biopsy confirmed reduced glycogen synthase activity. Ratio of active to inactive form of glycogen synthase was normal, suggesting reduced enzyme synthesis rather than synthesis of an inactive protein. Low hepatic glycogen content and mild to moderate liver steatosis were present. Plasma free carnitine concentrations decreased during fasting while esterified carnitine levels remained unchanged. In contrast to other cases, we twice observed an increase in blood glucose levels after administration of glucagon following 15 and 18 hours of fasting respectively (from 2.2 to 3.4 and 2.7 to 4.0 mmol/L respectively). Since her hepatic glycogen content was reduced, this might come from gluconeogenesis. At 13 years of age, our patient still has fasting hypoglycemia although to a lesser degree. Her growth and intellectual development remain normal. From our patient's clinical course and a review of the literature, we draw the following conclusions: (1) non specific symptoms after overnight fasting were the presenting complaint in 6/16, 3 cases were brought to medical attention because of incidental findings, family history led to the diagnosis in 7 cases, (2) fasting hypoglycemia (16/16) and reduced liver glycogen content (8/8) are constant features, (3) other frequent biochemical findings include hyperlactatemia with feeding (13/16) and fasting hyperketonemia (9/16) and hypotalaninemia (8/16); (4) glucagon response after feeding is usually absent (4/6) but can be observed (2/6); (5) liver steatosis was observed in 5/8 cases, (6) growth and development are usually normal (12/16 and 13/16 respectively).