A Case Of Mucolipidosis Type IV Identified Via Exome Slice; The Importance Of Utilizing Exome Slice For Difficult To Diagnosis Cases.

Rachel Li, MD[1], Allison T. Goodwin[2], Raymond C. Lewandowski[3].

[1]Virginia Commonwealth University Health System, Richmond, VA, USA,
[2]VCU Health, Richmond, VA,
[3]Virginia Commonwealth University Health System, Richmond, VA.

Mucolipidosis type IV (MLIV) (OMIM# 252650) is an autosomal recessive lysosomal storage disorder characterized by severe progressive psychomotor delay and ophthalmologic abnormalities (Schiffmann et al. Mucolipidosis IV. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993). Other features include characteristic MRI findings, iron deficiency anemia, and achlorhydria (Bach G. Mucolipidosis Type IV. Molecular Genetics and Metabolism. 2001;73(3):197-203). MLIV is caused by homozygous or compound heterozygous pathogenic mutations in MCOLN1 which encodes mucolipin-1. Alterations in mucolipin-1 result in the accumulation of lipids and proteins within cytoplasmic vacuoles (Wakabayashi et al. Mucolipidosis Type IV: an Update. Mol Genet Metab. 2011;104(3):206-213). MLIV is found with relatively high frequency within the Ashkenazi Jewish population although is pan ethnic and can be seen in all populations (Bargal et al. Mucolipidosis type IV: novel MCOLN1 mutations in Jewish and non-Jewish patients and the frequency of the disease in the Ashkenazi Jewish population. Hum Mutat. 2001;17(5):397-402). Here we present the case of a 7-year-old African American female who presented with global developmental delay, perinatal stroke, and abnormal brain MRI. At the time of presentation, she was noted to be non-verbal and functioning at the level of 2-year-old. She also had a history of seizures, ataxic gait, hand flapping, and hypertonia. MRI showed agenesis of the corpus callosum and delayed white matter myelination. Chromosomal microarray was obtained and showed a large region of homozygosity encompassing 5.9 percent of the human genome. There was initially a concern for Angelman or Rett syndrome given her ataxic gait, seizures, significant hand flapping, and profound speech delay but testing was obtained and was negative. At that point, an exome slice was obtained of the regions of homozygosity which identified homozygous pathogenic variants in MCOLN1 (c.379C>T) consistent with a diagnosis of MLIV. Even though this variant had not previously been reported, it was noted to be a nonsense variant that was predicted to result in protein truncation or nonsense mediated decay. Those with MLIV have been found to have normal levels of mucopolysaccharides, oligosaccharides, and lysosomal hydrolases (Wakabayashi et al. Mucolipidosis Type IV: an Update. Mol Genet Metab. 2011;104(3):206-213). Diagnosis can be made via skin biopsy which demonstrates membrane bound vesicles filled with granular material and concentric lamellar bodies, but this is invasive and difficult to obtain (Gowda et al. Mucolipidosis Type IV Due to Novel MCOLN1 Mutation. Indian J Pediatr. 2017;84(11):871-872). This fact, in addition to the variable phenotypic presentation, can make diagnosis of MLIV difficult. It is important to correctly diagnosis these patients as it can affect treatment guidelines, specifically regarding referral for ophthalmological evaluation. We propose that exome slice can be an important and useful diagnostic tool when used in cases of consanguinity noted on chromosomal microarray in difficult to diagnosis cases.

CMA->WES (sliced)

5.9% of the genome is >170Mbp, a giant loss of heterozygosity!