P2.026: Compound heterozygosis of a splice site and the common Ashkenazi Jewish mutation in GBE1 causes adult onset polyglucosan body disease.

Objective: To determine the genetic cause of glycogen branching enzyme (GBE) deficiency leading to late onset glycogenosis type IV

Background: Adult polyglucosan body disease (APBD) is a rare autosomal recessive disorder, caused by pathogenic mutations in glycogen branching enzyme gene (GBE1). Disease is characterized by urinary dysfunction, spastic paraplegia with vibration sense loss, peripheral neuropathy, and cognitive impairment. Because of the similarities, APBD is misdiagnosed with multiple sclerosis, benign prostatic hyperplasia, and rarely with ALS and dementia. Symptoms start at 4th or 5th decade of life, the most common mutation causing APBD is c.A986C found in Ashkenazi Jewish population substituting tyrosine with serine in 329th codon (p.Y329S). Deficiency of GBE causes poorly branched glycogen similar to starch found in plants. This alteration in structure makes polyglucosan precipitate in the cell adversely affecting the cell function.

Design/Methods: Patient we report here is a 60 year old man. He has mainly neurogenic bladder and minor difficulty in executive function. His gait is virtually normal with minor balance deficit. We measured biochemical activity of GBE in white blood cells and sequence the GBE1 gene and cDNA to present the aberrant splicing of mRNA.

Results: We have determined that patient has 8% of normal GBE activity due to two pathogenic heterozygous mutations c.A986C and c.691+2T>C, one substituting tyrosine with serine and the second affecting the proper splicing of mRNA.

Conclusion: APBD is an underdiagnosed disease, here we report the first time the occurrence of c.691+2T>C, mutation in an adult patient. This information is important for genetic diagnosis and management of the disease.

S42.006: An exon trap with proper poly-A site in the GBE1 is the common missing cause in Adult Polyglucosan Body Disease

Objective: Identify the underlying genetic cause of glycogen branching enzyme (GBE) deficiency in manifesting heterozygous patients of adult polyglucosan body disease (APBD).

Background: APBD is an autosomal recessive leukodystrophy caused by mutations in glycogen branching enzyme (GBE1). It is a late onset variant of glycogen storage disorder type-IV. Most patients are Ashkenazi-Jewish descendants, 70% of whom have homozygous GBE1 mutations. The remaining 30% are heterozygous for the p.Y329S mutation. The second mutation was not found until now in those patients in spite of whole-genome sequencing. This had raised the possibility that p.Y329S heterozygous cases were somehow ‘manifesting heterozygotes’.

Design/Methods: We studied 16 APBD patients who are heterozygous for p.Y329S mutation in GBE1 with yet have unlikely low GBE activity with no other known mutation in 16 exons.

Results: GBE1 mRNA has been reverse transcribed and sequenced, all manifesting heterozygous patients were homozygous for c.986A>C mutation substituting tyrosine with serine. The mRNA transcript from the other allele was missing the exon 16 and 3'UTR. GBE encoded by this copy was degraded in the cell causing the further decrease of enzyme activity from 18% to 8%. Sequencing of polyA tailed mRNA revealed an exon splice site that changes last exon and 3'UTR.

Conclusion: We now identified this deep-intronic mutation, which acts as a gene-trap, creating an ectopic last-exon, 3'UTR and degraded protein. This second-most common APBD mutation now explains all Ashkenazi-Jewish cases and a molecular mechanism for manifesting heterozygosis.