P-082 - N370S/RECNCIL GENOTYPE-PHENOTYPE CORRELATION IN A COHORT OF 197 ARGENTINEAN GAUCHER DISEASE PATIENTS.

Drelichman GI [1], Fernández-Escobar N [1], Soberon BC [1], Ruan J [2], Belinsky B [2], Schenone AB [3], Christmann A [1], Larroude M [4], Aguilar G [4], Mistry P [2] et al.

(1) Hospital de Ninos Ricardo Gutierrez, ciudad autonoma de Buenos Aires, Argentina. (2) Yale University School of Medicine, New Haven, CT, United States. (3) Laboratorio de Neuroquimica Dr N A Chamoles, ciudad autonoma de Buenos Aires, Argentina. (4) Centro de Diagnostico Dr Rossi, Enrique, ciudad autonoma de Buenos Aires, Argentina. Ciudad de Buenos Aires-Argentina. bsoberon@live.com

INTRODUCTION: Gaucher disease (GD), the most common lysosomal storage disorder, is caused by homozygous or compound heterozygous mutations in GBA gene that results in defective lysosomal enzyme glucocerebrosidase (EC 3.2.1.45). The existence of pseudogenes in 1q21 GBA loci not only results in increased risk of generating complex alleles, but also hinders accurate GBAmutation analysis in the clinic and the genetic counseling of GD. ***OBJECTIVES:*** To know argentinean GD patients genotype, to analyze the genotype-phenotype correlation and evaluate its correaltion with bone disease severity. ***METHODS:*** We developed PacBio long read GBA deep sequencing to overcome the standard genotyping involving screen for common mutations or analysis of full coding regions, and furthermore, to maximize coverage depth and haplotype GD patients. We applied Sanger sequencing for validation of genotype ascertained by PacBio sequencing. These approaches are applied to genotype and haplotype a large cohort of Argentinean GD gDNA samples. ***RESULTS:*** 144/184 (78.3%) of the evaluable samples were successfully genotyped and phased in identifying disease-causing mutations as allelic variants. The mutation N370S (79.8%) was the most frequent in our GD argentine patients. The genotype N370S / RecNcil (47.2%) was the most frequent followed by N370S/L444P (9.7%). Nine novel mutations were identified. Comparing our findings with the rest of the world we found that: In Argentina the genotype N370S/L444P (9.7%) is less frequent than in Europe (21.9%) and USA (14.3%) (Gaucher International data) and the Genotype N370S/RecNcil is more frequent in Argentina 47.2% than the rest of Latin America (2.4%). The Genotypes N370S/N370S and L444P/L444P are also less frequent in Argentina than Europe and USA. The genotype N370S /RecNcil is associated with a more serious phenotype with early bone disease (p=0.005), such as the one found in the argentinean population. ***CONCLUSIONS:*** Higher coverage depth and long-read whole GBA gene SMRT sequencing are essential to GD clinical diagnosis and genetic counseling. The most frequent genotype was N370S/ RecNcil in 47.2 % of the patients in contrast with other publications. The presence of the N370S/RecNcil mutation appeared to be correlated (p= 0.05) with the presence and severity of bone disease.