Classic Galactosemia: Phenotypic and Molecular Features in Southern Brazil

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Introduction

Classic Galactosemia [CG] is an inherited metabolic disorder resulting from profound functional impairment of Galactose-1-Phosphate Uridyltransferase [GALT]. Newborn screening for CG is not widely available, leading to underdiagnosis and late access to reference centers. We aim to characterize the phenotype and genotyping of patients with CG from Southern Brazil.

Methods

An observational, retrospective study with convenience sampling was conducted. Data was obtained through medical records review.

Results

Nineteen individuals were included (male=10; mean age at inclusion=11.3y; alive=18; ancestry: Caucasian=55%; Native American=33%; and African=11%) from 17 families. Four unrelated patients had consanguineous parents. Cities of Origin are shown in Figure 1. Sixteen patients had acute neonatal illness, one receiving post-mortem diagnosis by genetic analysis. Three were detected by expanded NBS (private health sector).

Late complications were Global Developmental Delay or Intellectual Disability in 12/18, Language Delay in 14/18, Psychiatric Disorders in 6/18, Neurological Impairments in 7/18, Cataracts in 7/18, and Premature Ovarian Insufficiency (POI) in 3/4 adult female patients. One patient had a successful pregnancy and did not present POI symptoms in the last medical assessment (30y). Eleven were already genotyped, yielding 9 different pathogenic variants, with the identification of three novel variants in GALT gene: c.164G>T[p.Gly55Val], and 2 in cis-variants: c.90dup;529A>G or p.[His31Alafs*10;Met177Val]; which we call the Kaingang allele [K allele], present in all Kaingang people of our sample (Figure 2). The two variants with higher allelic frequency were the K allele (36%) and p.Gln188Arg (23%).

GALT

c.90dup  c.529A>G

Figure 2: K allele variants, found in all Kaingang people of our sample. c.90dup is a frameshift duplication that is predicted to cause nonsense mediated mRNA decay. c.529A>G, although described as p.[Met177Val], is not expected to have any effects in this allele. Transcript: NM_000155

Conclusion

The study of CG patients in Southern Brazil revealed complex clinical and genetic features and identified a possible higher prevalence in Native Americans. The expansion of newborn screening, which includes CG, was sanctioned in Brazilian Public Health System. The implementation is estimated to occur up to May 2022. Thus, it will be crucial to proceed in the characterization of CG Brazilian patients and determination of populational isolates and founder effects.

Reference: